

# IYRC 2021

International Young Researchers' Conference



In Partnership with the Columbia University Vagelos College of Physicians and Surgeons Global Health Organization

October 16th and 17th, 2021

[info@the-iyrc.org](mailto:info@the-iyrc.org)  
[www.the-iyrc.org](http://www.the-iyrc.org)

**Proceedings of the 5th International Young Researchers' Conference (IYRC)**

**October 16<sup>th</sup> and 17<sup>th</sup>, 2021**

Edited by

Elizabeth Feldeverd & Paul Lewis

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info@the-iyrc.org

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## Acknowledgements

This report is based on the International Young Researchers' Conference (IYRC) that was made possible through sponsorships and collaborations with Harvard College Japan Initiative (HCJI), Harvard College VISION, Tokyo Academics, and Columbia University Vagelos College of Physicians and Surgeons (VP&S) Global Health Organization (GHO) and the Program for Education in Global and Population Health under the Department of Medical Education.

The conference was organized and co-directed by Paul Lewis, Elizabeth Feldever, and Tsuyoshi Domoto. Advisors for the program were Dr. William Turner and Dr. Kim Hekimian. Several Faculty and physicians from Columbia VP&S provided lectures and guidance for students including Dr. Benjamin Lebwohl, Dr. Bernard P. Chang, Dr. Jennifer Manly, Dr. Joyeeta G. Dastidar, Dr. Maria de Miguel, and Dr. Christopher Winfree. Staff support was provided by Francisco Gaddi, Jr. Additionally, the program had special volunteers as standardized patients, mentors, and facilitators including Columbia VP&S students: Amy Lipman'24, Elyse Decker'25, Joshua Dawson'25, Jackie Dragon'24, Kavya Rajesh'24, and Teja Gopal'24; students from other universities: Akshara Shankar (U.C. Berkeley), Angie Chen (Northeastern University), Ashley Cooper (Harvard College), Christopher Holden-Wingate (U.C. Davis), Diana Gerberich (Johns Hopkins), Emily Tran (Stanford University), Kelsey Ichikawa (Harvard College), Megan Hoang (U.C. Davis), and Onyinyechi Owo (Dartmouth College); and high school student Vision Scholars: Arthur Liang (New York), Gawon Yoo (Massachusetts), Hannah Pescaru (Illinois), Juan Sandoval (Mexico), Marlyn Li (Massachusetts), Rhea Werner (Australia), and Sara Maggio (Illinois).

We would like to especially thank our 97 high school students from 12 countries who participated in the intensive 10-week summer program. They learned from physicians, researchers, and medical students at Columbia University VP&S. Students enjoyed diverse experiences: they learned how to take a patient history, interviewed several standardized patients, engaged in ethical discussions, had conversations about narrative medicine, and studied various systems of human anatomy. In addition to the clinical aspects of the program, students learned research methods for finding sources, analyzing data, and writing a manuscript. Students came from a variety of backgrounds such as low-income, single parent households, or families where they will be the first to graduate college. They identify as Asian (53%), Black and Latinx (24%), and White (23%). 68% use She/Her/Hers pronouns, 31% use He/Him/His, and 1% They, Them, Theirs pronouns. Countries represented included Australia, Bahrain, Cameroon, Canada, Hong Kong, Japan, Mauritius, South Korea, Turkey, the United Kingdom, and the United States of America.

## Organizing Committee

### Founder



Paul M. Lewis

Harvard College | A.B.

Columbia University VP&S | M.D. Candidate

Paul M. Lewis is a second-year medical student at Columbia University Vagelos College of Physicians and Surgeons. He holds a Bachelor of Arts degree from Harvard College where he concentrated in Neurobiology with a secondary in Global Health and Health Policy. Paul was a recipient of the Finley Fellowship from Harvard to spend a postgraduate year in Japan to learn about end-of-life care. While there, he founded the International Young Researchers' Conference. At Columbia University, he co-leads the American Association of Neurological Surgeons, the Allen O. Whipple Surgical Society, and the Global Health Organization.

#### Directors

Paul M. Lewis  
Elizabeth Feldeverd  
Tsuyoshi Domoto

#### Organizational support

Francisco Gaddi, Jr.  
Athena Dionisio

#### Reviewers

Hayden Mueller  
Roman Casco  
Kaitlyn Cyprian  
Yibo Sun  
Jonathan Hill  
Libby Ruth Mullin  
Nourhan Ibrahim  
Lok Yong Chia  
Kelly Friedman

#### Sponsors, Partners, and Collaborators

Columbia University Vagelos College of Physicians and Surgeons Global Health Organization  
Columbia University the Program for Education in Global and Population Health  
Columbia University the Department of Medical Education  
Harvard College Japan Initiative  
Harvard College VISION  
Tokyo Academics

## Keynote Speakers

### Dr. Daniel K. Owens



Daniel K. Owens earned a BSc degree with a concentration in biochemistry from East Tennessee State University where he first began research into natural products and flavonoid metabolism by developing a novel assay system for flavanone-3-hydroxylase. He continued working with flavonoids in the lab of Brenda Winkel at Virginia Tech and was awarded his PhD for examining the labile dioxygenase enzymes involved in flavonol biosynthesis in *Arabidopsis thaliana* with a particular focus on the flavonol synthase isozyme family. He then began a postdoctoral position in the lab of Cecilia McIntosh where glucosyltransferase enzymes with the potential to influence flavor chemistry and other aspects of metabolism in Citrus species were identified and thoroughly characterized. Subsequently, he moved to a plant physiologist postdoctoral position with the USDA-ARS Natural Product Utilization Research Unit in Oxford, MS where natural products were investigated as herbicide leads and herbicide resistant crop plants were characterized in the labs of Franck Dayan and Stephen Duke. Daniel is currently an assistant professor in Molecular Biosciences and Bioengineering at the University of Hawaii - Manoa in Honolulu, HI where his lab is investigating the potential of flavonoid enzymes to interact within a metabolon in citrus as well as agricultural, nutritional, and pharmaceutical applications of plant natural products.

### Dr. Christopher Winfree



Dr. Winfree grew up in Jupiter, Florida, and attended Dartmouth College, where he graduated with High Honors in Chemistry. After completing medical school at Columbia University College of Physicians and Surgeons in New York, he joined the Department of Neurological Surgery at Columbia University as a resident. Following residency, he completed a fellowship in peripheral nerve surgery in New Orleans, Louisiana, and then a second fellowship in functional and stereotactic neurosurgery in Portland, Oregon. Currently, Dr. Winfree is an Assistant Professor of Neurological Surgery at the College of Physicians and Surgeons in New York City where he specializes in peripheral nerve surgery, peripheral nerve cancer surgery, nerve and muscle biopsies, pain neurosurgery, and spasticity. His research interests include the use of peripheral nerve transfers to treat spinal cord injury, and the use of neurostimulation to treat chronic pain disorders. He is a member of several different professional organizations, including the American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), American College of Surgeons (ACS), New York State Neurosurgical Society, North American Neuromodulation Society (NANS), Neurosurgical Society of America (NSA), New York Presbyterian Society of the Alumni, Society of Neurological Surgeons (SNS) Boot Camp Committee, and the CNS Self Assessment in Neurological Surgery (SANS) Editorial Board. He recently completed his term as President of the AANS / CNS Joint Section on Pain.

## Full Conference Schedule

<b>October 16th</b>		
9:45 AM	OPENING TALK	
10:00 AM	Juan Sandoval	Mexico's National Electoral Institute: Lessons from Current Progress, Shortcomings, and Citizen Response.
10:15 AM	Yuto Abe	Diversity, Equity, and Inclusion and Representations of Japanese American History at Rye Country Day School
10:30 AM	Aashika Jagadeesh	FreeFeed: Combating Degenerate Feedback Loops With Linguistic Inferences From Human Interactions On Social Media
10:45 AM	Annika Viswesh	Investigating the Sequence Elements that Affect the Translation Efficiency of the Fungal Pathogen Histoplasma Capsulatum
11:00 AM	Break	
11:15 AM	Stefan Iordache	The Effects of Digital Media Use on Youth Brain Development – A Systematic Review
11:30 AM	Vinay Kalva	The Impact of Low Farming Yields in Sub-Saharan Africa on Maternal Mortality and Mortality of Children Under the Age of 5
11:45 AM	Jonathan Wun	NIH Research Funding For Palliative Care And COVID-19
12:00 PM	Reeya Sannake	A Systematic Review of Communication and Health Literacy Barriers in Healthcare
12:15 PM	Tara Suri	Retinal Detachment Is in The Eye of The Beholder
12:30 PM	Lunch	
1:00 PM	<b>KEYNOTE SPEECH</b>	<b>DR. DANIEL K. OWENS</b>
2:00 PM	Break	
2:15 PM	Anita Osuri	Biological Warfare's Role in Colonization
2:30 PM	Catherine Alexis	Correlation of Race and Income with COVID-19 Vaccination Status in Monroe County, New York
2:45 PM	Momo Hayashi	Expression analysis of glucan synthase in edible mushrooms Lentinula edodes and Pleurotus eryngii and their potential for wound-healing applications
3:00 PM	Christopher Huang	Disparities in Access to Primary Dental Care: A Systemic Review
3:15 PM	Areeba Inam	How Does Graft Versus Host Disease React to the Heart, Lungs, and Liver After an Allogeneic Stem Cell Transplant?
3:30 PM	Break	
3:45 PM	Shani Getz	Increase in Relative Highway Fatalities During the COVID-19 Pandemic with Respect to Driver Age Distribution
4:00 PM	Erin Wong	The role of neuroeconomics in advertisement: a systematic review
4:15 PM	Suhana Singh	Evaluating general ubiquitination techniques to find a method effective for AChR autoantibodies as a potential treatment of Myasthenia Gravis
4:30 PM	Marko Zimic	Constricted: My Uncle and His Struggle with COPD
4:45 PM	Jihyung Kim	Escalating the Quantity of Medical Data Using CTGAN: Diabetes Dataset

5:00 PM	Break	
5:15 PM	Case studies	
5:45 PM	Dinner	
6:15 PM	Edison Suzuki	Evaluation of Kyogen costume storage environment and calculation of proper temperature setting for energy conservation effect using fungal index
6:30 PM	Sungjoon Kang	In Silico Analysis of an Epitope-Based Bladder Cancer Vaccine
6:45 PM	Tanisa Goyal	Association Between BMI and COVID-19 Clinical Outcome Severity: A Systematic Review Comparing Data from Asian and Western Countries
7:00 PM	Eugenia Calvo Prieto	Cognitive-behavioural therapy (CBT) for reducing implicit biases among healthcare professionals
7:15 PM	Kathy O'Shea	Characterization of lupeol, linalool, and squalene synthase expression within floral, leaf, and seed tissues of <i>Camellia japonica</i> and <i>Camellia sasanqua</i> .
7:30 PM	Break	
7:45 PM	Emily Cho	Can Two People Process Different Things Based on Differences in Cultural Identity?
8:00 PM	Naoya Kobayashi	Phenylalanine Ammonia-lyase 1 (PAL1) Expression During Cold Stress in Two Japanese Tomato Varieties
8:15 PM	Ashley Seong	Human visualization of brain tumor classifications using deep CNN: Xception + BiGRU
8:30 PM	Seoyoon Choi	Applying Constructivism in Neurodiverse Classrooms
8:45 PM	Aryan Chaudhary	Islamic Feminism's relation to the Western Feminist movement and Sharia Law
9:00 PM	Break	
9:15 PM	Sarah Yim	Rice Leaf Disease Classification Using Deep Transfer Learning Convolutional Neural Network: MobileNet + Bidirectional GRU
9:30 PM	Peyton Yamanaka	S-BRATA and Japan: A Novel Art Therapy Framework for the Treatment of ASD and Comorbid SID
9:45 PM	Kevin Slattery	From Pagodas to Printed Homes: Exploring the Flexural Strain, Deflection, and Relative Strength of 3D Printed Japanese Joinery
10:00 PM	Song Jeong Gyoun	Telemedicine: Where the future lies
10:15 PM	Ria Choi	Research about antimicrobial mask using Alginic acid membrane
10:30 PM	Haebin Jung	How Cram Schools Perpetuate the Cycle of Poverty in South Korea

### October 17th

10:00 AM	Reminders	
10:15 AM	Ralph Ballard	Evaluation of rhGH therapy in treating small stature as a result of being born small for gestational age (SGA) without catch-up growth
10:30 AM	Napoleon Star	Evaluating candidate IRAP inhibitors in Ginkgo biloba extract and their potential for cognitive enhancement
10:45 AM	Zoe Atherton	The psychosocial impacts of social isolation caused by public health strategies as a preventative measure of the spread of the Coronavirus Disease 2019 (COVID-19) on elderly adults: A systematic review

11:00 AM	Wataru Hoshi	Systematic review with meta-analysis of fall detection systems for elderly care: perspectives for an aging population in Japan
11:15 AM	Jihong Jung	From DIO2 Genotype to Personalized Medication
11:30 AM	Emily Tanaka	Japanese student movements of the 1960s and 2010s: comparing Zenkyoto and SEALDs
11:45 AM	Break	
12:00 PM	<b>KEYNOTE SPEECH</b>	<b>DR. CHRISTOPHER WINFREE</b>
1:00 PM	Lunch	
1:30 PM	Gregory Guyumdzhyan	The Varying Misconceptions and True Effects of Videogames on Psychological Functioning
1:45 PM	Kevin Zhang	Stress and Isolation: The Effects of a Remote Learning Environment on Adolescent Emotional Development
2:00 PM	Daniel Pyeong Kang Kim	Finding ESG's Aptitude for Projecting Financial Value by Novel Machine Learning
2:15 PM	Audrey Czarnecki	Brain Reactions to Film Watching
2:30 PM	Annesha Dey	Exploring the effect of music therapy in elders living in hospice and palliative care
2:45 PM	Break	
3:00 PM	Grace Molano	Memories Slipping Away: My Grandmother and Dementia
3:15 PM	Inselbag Lee	The Evolving U.S. Policy Toward Asylum Seekers
3:30 PM	Leo Sun	Climate change and allergic respiratory disease: an overview of effects on children's health
3:45 PM	Fatima Bagom	Impact of Weight Stigma on Obese Women and Their Reproductive Health
4:00 PM	Jeffrey Li	Uses of Drone & UAV Technology in Accessing Healthcare: The Case of Madagascar
4:15 PM	Break	
4:30 PM	Xuetao Wu	Perception of sexuality and gender identity in anime: How positive representations could be used to combat LGBTQ+ discrimination.
4:45 PM	Julia Moosikasuwon	My Grandparents' Battle Against COVID-19
5:00 PM	Mao Motoyoshi	Investors! Meddle in Medellin!
5:15 PM	Edward Cho	Effect of strength training on bone growth and development in children and adolescents
5:30 PM	Misaki Tatsumi	Studies on Innovative Application of Immersive Virtual Reality in Medical Field: a Possibility of Full-Dive Virtual Reality
6:30 PM	Cocoro Motoyoshi	"Natalie is a Late Bloomer."

## Contributed papers

### Research

**13** Diversity, Equity, and Inclusion and Representations of Japanese American History at Rye Country Day School  
Yuto Abe

**20** Correlation of Race and Income with COVID-19 Vaccination Status in Monroe County, New York  
Catherine Alexis

**26** The Psychosocial Impacts of Social Isolation Caused by Public Health Strategies as a Preventative Measure of the Spread of the Coronavirus Disease 2019 (COVID-19) on Elderly Adults: A Systematic Review  
Zoe Atherton

**34** Impact of Weight Stigma on Obese Women and Their Reproductive Health  
Fatima Bagom

**41** Evaluation of rhGH Therapy in Treating Small Stature as a Result of Being Born Small for Gestational Age (SGA) Without Catch-Up Growth  
Ralph Ballard

**50** Cognitive Behavioral Therapy (CBT) for Reducing Implicit Biases Among Healthcare Professionals  
Eugenia Calvo Prieto

**61** Islamic Feminism's Relation to the Western Feminist Movement and Sharia Law  
Aryan Chaudhary

**67** Can Two People Process Different Things Based on Differences in Cultural Identity?  
Emily Cho

**73** Myth-Busting: Is the Usage of Strength Training in Pubescents Actually Harmful and Does It Stunt Growth?  
Edward Cho

**80** Applying Constructivism in Neurodiverse Classrooms  
Seoyoon Choi

Research About Antimicrobial Mask Using Alginic Acid Membrane  
Seoin Choi

**87** Brain Reactions to Film Watching  
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**94** Exploring the Effect of Music Therapy in Elders Living in Hospice and Palliative Care  
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**102** Increase in Relative Highway Fatalities During the COVID-19 Pandemic with Respect to Driver Age Distribution  
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**109** Association Between Bmi and COVID-19 Clinical Outcome Severity: A Systematic Review Comparing Data from Asian and Western Countries  
Tanisa Goyal

**116** The Varying Misconceptions and True Effects of Videogames on Psychological Functioning  
Gregory Guyumdzhyan

**122** Expression Analysis of Glucan Synthase in Edible Mushrooms Lentinula Edodes and Pleurotus Eryngii and Their Potential for Wound-healing Applications  
Momo Hayashi

**127** Systematic Review with Meta-Analysis of Fall Detection Systems for Elderly Care: Perspectives for an Aging Population in Japan  
Wataru Hoshi

**134** Disparities in Access to Primary Dental Care: A Systematic Review  
Christopher Huang

**143** How Does Graft Versus Host Disease React to the Heart, Lungs, and

Liver After an Allogeneic Stem Cell Transplant?  
Areeba Inam

**150** The Effects of Digital Media Use on Youth Brain Development - A Systematic Review  
Stefan Iordache

**156** FreeFeed: Combating Degenerate Feedback Loops with Linguistic Inferences from Human Interactions on Social Media  
Aashika Jagadeesh

**165** From DIO2 Genotype to Personalized Medication  
Jihong Jung

**172** How Cram Schools Perpetuate the Cycle of Poverty in South Korea  
Haebin Jung

**179** The Impact of Low Farming Yields in Sub-Saharan Africa on Maternal Mortality and Mortality of Children Under the Age of 5  
Vinay Kalva

**189** In Silico Analysis of an Epitope-Based Bladder Cancer Vaccine  
Sungjoon Kang

**201** Excavating ESG's Aptitude for Projecting Financial Value by Novel Machine Learning  
Daniel Pyeong Kang Kim

**208** Escalating the Quantity of Medical Data Using CTGAN: Diabetes Dataset  
Jihyung Kim

**213** Phenylalanine Ammonia-lyase 1 (PAL1) Expression During Cold Stress in Two Japanese Tomato Varieties  
Naoya Kobayashi

**218** The Evolving U.S. Policy Toward Asylum Seekers  
Inselbag Lee

- 224** Uses of Drone & UAV Technology in Accessing Healthcare: The Case of Madagascar  
Jeffrey Li
- Investors! Meddle in Medellin!  
Mao Motoyoshi
- 244** Characterization of Lupeol, Linalool, and Squalene Synthase Expression Within Floral, Leaf, and Seed Tissues of Camellia Japonica and Camellia Sasanqua.  
Kathy O'Shea
- 250** Biological Warfare's Role in Colonization  
Anita Osuri
- 254** Mexico's National Electoral Institute: Lessons from Current Progress, Shortcomings, and Citizen Response  
Juan Sandoval
- 261** A Systematic Review of Communication and Health Literacy Barriers in Healthcare  
Reeya Sannake
- 267** Human Visualization of Brain Tumor Classifications Using Deep CNN- Xception + BiGRU  
Ashley Minsuh Seong
- 276** Evaluating If Ubiquitination of AChR Autoantibodies Could Be an Effective Method to Treat Myasthenia Gravis  
Suhana Singh
- 283** From Pagodas to Printed Homes: Exploring the Flexural Strain, Deflection, and Relative Strength of 3D Printed Japanese Joinery  
Kevin Slattery
- Telemedicine: Where the Future Lies  
Jeong Gyoun Song
- 292** Evaluating Candidate IRAP Inhibitors in Ginkgo biloba Extract and Their Potential for Cognitive Enhancement  
Napoleon Star
- 297** Climate Change and Allergic Respiratory Disease: An Overview of Effects on Children's Health  
Leo Sun
- 310** Evaluation of Kyogen Costume Storage Environment and Calculation of Proper Temperature Setting for Energy Conservation Effect Using Fungal Index  
Edison Suzuki
- 319** Japanese Student Movements of the 1960S and Their Contemporaries: Comparing Zenkyoto and SEALDS.  
Emily Tanaka
- 326** Studies on Innovative Application of Immersive Virtual Reality in Medical Field: a Possibility of Full Dive Virtual Reality  
Misaki Tatsumi
- 335** Investigating the Sequence Elements That Affect the Translation Efficiency of the Fungal Pathogen Histoplasma Capsulatum  
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- 344** The Role of Neuroeconomics in Advertisement: A Systematic Review  
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Xuetao Wu
- 363** NIH Research Funding for Palliative Care and Covid-19  
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Peyton Yamanaka
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- Health Narratives
- 232** Memories Slipping Away: My Grandmother and Dementia  
Grace Molano
- 236** My Grandparents' Battle Against COVID-19  
Julia Moosikasuwana
- 241** Natalie Is a Late Bloomer.  
Cocoro Motoyoshi
- 304** Retinal Detachment Is in the Eye of the Beholder  
Tara Suri
- 393** Constricted: My Uncle and His Struggle with COPD  
Marko Zimic

## Award Winners

The IYRC had many amazing presentations during the conference weekend. We were greatly impressed with the quality, dedication, and commitment in producing these diverse projects. The students have all truly accomplished amazing work with writing a manuscript approved by reviewers and presenting at an international conference.

Each conference, the IYRC awards seven special honors for the research projects. After tallying the scores from our reviewers who read the papers and watched the recordings, we are pleased to announce the results of the Fall 2021 IYRC research project awards:

**Best overall project:** Anita Osuri

- Biological Warfare's Role in Colonization

**Best Social Sciences and Humanities Paper:** Xuetao Wu

- Perception of Sexuality and Gender Identity in Anime: How Positive Representations Could Be Used to Combat LGBTQ+ Discrimination

**Best Social Sciences and Humanities Presentation:** Gregory Guyumdzhyan

- The Varying Misconceptions and True Effects of Videogames on Psychological Functioning

**Social Sciences and Humanities Honorable Mention:** Haebin Jung

- How Cram Schools Perpetuate the Cycle of Poverty in South Korea

**Best STEM Paper:** Christopher Huang

- Disparities in Access to Primary Dental Care: A Systematic Review

**Best STEM Presentation:** Leo Sun

- Climate Change and Allergic Respiratory Disease: An Overview of Effects on Children's Health

**STEM Honorable Mention:** Jonathan Wun

- NIH Research Funding for Palliative Care and Covid-19

We also had a case study competition with 4 winners:

**First Place - Team S**

- "The Financial and Psychological Barriers to Senior Care" - Shani Getz (Massachusetts), Anita Osuri (New Jersey), and Reeya Sannake (Michigan)

**Second Place - Team O**

- "Trying to Lower the Cost of Healthcare: Why are We Getting Nowhere" - Kevin Zhang (New York) and Xuetao Wu (Massachusetts)

**Third Place Tie - Team N & Q**

- "Barriers of Psychiatric care" - Ella (Taeun) Kim (California), Kristen Chun (Massachusetts), and Saia Kalash (New York)
- "The Inequality of Vaccination" - Audrey Czarnecki (Virginia), Tracey Maina (Massachusetts), and Safia Syed (Maine)

# Diversity, Equity, and Inclusion and Representations of Japanese American History at Rye Country Day School

Yuto Abe

Rye Country Day School, United States  
yutoabe0228@gmail.com

## Abstract

This paper explores ways in which Diversity, Equity, and Inclusion (DEI) practices at my high school, Rye Country Day School (RCDS), can be improved to recognize minority students, with a particular focus on Japanese and Japanese American students. RCDS is an affluent, private institution located in a suburban neighborhood in New York State, USA, where sixty-four percent of the student body identifies as white. RCDS offers an Advanced Placement United States History (APUSH), but the textbook it uses, *American History* by Alan Brinkley, barely touches on Japanese and Japanese American history outside of World War II. Through primary and secondary historical sources, the paper sets out to uncover the hidden stories in Japanese American history.

As an autoethnography, this research offers various constructive ideas for RCDS as an institution by looking into the current initiatives that the school has taken to create a more welcoming environment for minorities and identifying spaces for further support for the student body. Centering my research on RCDS comes with the hope that it will support my school in its efforts to ensure that students receive an education that allows them to explore beyond what is written on the surface of textbooks.

By considering RCDS as a case study, I hope to inspire similar institutions to re-examine their curriculum and put historical representation at the

forefront of their DEI initiatives. In an increasingly polarized political climate, the anti-racist work initiatives suggested can be applied more widely for the benefit of students everywhere.

*Keywords: Diversity, Equity, and Inclusion (DEI); Japanese/Japanese American History; Autoethnography; anti-racism; American History; Case study*

## Introduction

In many United States history classes offered across secondary schools in the United States, Japanese and Japanese American history is often, at most, contained to World War II and related events. My experience taking Advanced Placement United States History (APUSH) at Rye Country Day School, a private institution located in an affluent neighborhood in New York State where sixty-four percent of the student body identifies as white (Rye Country Day School, n.d.), became my impetus to embark on this research. I was assigned an end-of-the-year project, in which the topic that I chose was the historiography of Japanese American internment during WWII. As I was researching, I discovered details that the APUSH exam excluded, and was eager to learn more. Japanese history in the U.S. extends beyond internment. By taking a close historical view into anti-Japanese sentiments and juxtaposing it with the current climate at RCDS, I hope to raise awareness in my school community about the importance of historical representation.

In doing so, I also hope to support my school in its efforts to ensure that students receive a comprehensive education that explores beneath the surface of texts and allows them to unfold the raw, collective memories of our nation's history. This paper first aims to chronologically examine the historical experiences of Japanese immigrants and Japanese Americans in the United States from the early 20th century to the developments of model minority narratives of Japanese and Japanese Americans during the mid-20th century. Then, this paper identifies the extent to which Japanese and Japanese Americans are described in the APUSH textbook at RCDS and identifies spaces where the school can improve as it carries on its Diversity, Equity, and Inclusion (DEI) mission. Finally, the paper seeks to connect the past to the present through contemplating the historical implications of occurrences affecting the larger Asian, Asian American, and Pacific Islander (AAPI) community in the United States with the onset of the Coronavirus pandemic.

*Representation of Japanese/Japanese American history in American History by Alan Brinkley*  
AMERICAN HISTORY by Alan Brinkley, the textbook used in the AP United States History course at RCDS, contains a two-page section for the "Internment of Japanese Americans" within a larger chapter about the Second World War (Brinkley, 2014).

The section starts with a comparison of the First World War with the second, claiming that the federal government violated fewer civil liberties in controlling seditious acts and that ethnic or cultural hostilities were less evident during the second war. However, the textbook explains that the greatest exception to the general societal atmosphere of tolerance to racial difference during WWII was the treatment of the "small, politically powerless group of Japanese Americans" (Brinkley, 2014 pg. 720). Brinkley's textbook describes in depth the various developments concerning Japanese Americans and their experiences during WWII but offers

limited glimpses into the experiences of Japanese and Japanese Americans prior to and following the historic internment.

### *Rise of Anti-Japanese Sentiments in the Early 20th Century*

Increasing numbers of Japanese immigrants entered California after the enactment of the 1882 Chinese Exclusion Act, which forced employers in the agricultural industry to suspend ready access to cheap labor. In ten years, the Japanese population in the state grew to exceed ten thousand (Molina, 2006, p. 50). Soon, with their arrival to the U.S., the Japanese replaced the positions of Chinese immigrants, inheriting much of the racism and exclusion that had devastated the Chinese community before Japanese entry. During the 1910s and 1920s, anti-Japanese sentiments rooted themselves in public health in the U.S. Specifically in Los Angeles, where the department of public health began blaming the Japanese for the spread of communicable diseases. Public health officials began stigmatizing Japanese as "unsanitary" and "ignorant classes" as they believed that Japanese presence led to the transmission of illnesses brought by them to whites (Molina, 2006, p. 53). Thus, in echoing the nation's agitation over the threat of cultural, political, and economic instability due to increasing Japanese immigration, the Los Angeles Health Department racialized public health to disadvantage Japanese immigrants while attempting to promote its reputation among the American public. Similarly, states such as Oregon and Washington learned of the prejudice and actively contributed to the nativistic attitude towards the Japanese residing there. As Kristofer Allerfeldt writes in his work *Race and Restriction: Anti-Asian Immigration Pressures in the Pacific North-west of America during the Progressive Era, 1885-1924* "prejudice is often more potent where the threat is perceived rather than actual. In this case, the imagined, bestial, 'Yellow Devil' could be made more threatening than the reality of a gang of submissive coolies" (Molina, 2006, p. 58). The

strong work ethic and generally acquiescent nature—as perceived by white employers—of Japanese workers may have allured ambitious employers. Yet, these exploited workers were compensated less by their employers than other workers merely for their racial background, elucidating one of the most pervasive forms of racism that the Japanese encountered upon their settlement. Thus, while California’s responsibility in the enactment of the 1924 Immigration Act, which banned entry of Japanese immigration, is undoubtable, the northwest must bear a large share of the responsibility for the exclusionary attitude towards the Japanese (Allerfeldt, 2003, p. 72).

#### *Japanese American Citizens League leading up to and during World War II*

The bombing of Pearl Harbor left a lasting mark within the Japanese American community in the U.S. as political authority shifted from the first-generation immigrants, the Issei, to its second generation, the Nisei. Combined with the Nisei’s vexation over their political and economic subordination was the increasingly visible cultural chasm between the two generations—the Issei, while choosing the U.S. as their permanent home, tended to “remain culturally more Japanese than American” whereas their children, while being exposed to the “Japanese language, tradition, and thought patterns at home or Japanese school, were nonetheless more American than Japanese” (Spickard, 1983, p. 150). Moreover, what distinguished and, at the same time, separated the Nisei apart from their older generation was their stronger desire to adopt an American middle-class lifestyle, their greater command of American skills, their lack of Japanese skills, and a “broader intellectual perspective” (p. 150). The Nisei slowly emerged as a legitimate political entity through the Japanese American Citizens League (JACL), an organization founded in 1929 that claimed to represent the interests of Japanese Americans. The Nisei felt strongly that they were ‘more’ American than their parents’ generation. After the

attack on Pearl Harbor, FBI agents began interning “... all the Issei who looked like community leaders or had tangible connections with Japan (Spickard, 1983, p. 156).” Nisei officers of the JACL served as informants for the FBI. While leaders may have convinced several state and local officials of Nisei’s patriotism to the U.S., the detainment of the Issei and the ultimate internment of the Nisei eclipsed any hopes of political success that JACL leaders anticipated. When Japanese Americans most relied on the Nisei JACL, its leaders failed them. While hundreds of Japanese Americans living in LA lost their jobs in private businesses and local and state governments from 1941 to 1942, and others were physically beaten or extorted by thieves posing as government officials, the JACL did not respond. Most importantly, when faced with the unavoidable fate of internment, the JACL “did not make a sound other than to tell their constituents: ‘We are going into exile as a patriotic duty’” (Spickard, 1983, p. 169).

Until the end of World War II, the JACL did not reappear as a powerful entity in the Japanese American community. Some Japanese Americans began to protest, arguing that leaders of the JACL were simply pursuing their own personal glory through their obliging stance prior to and during internment. It is reasonable to acknowledge that JACL leaders decided to be complacent to keep away from literal bloodshed, but this does not exactly justify the lack of response to the persecution that many Japanese Americans faced before their forced removal.

#### *Post War Racial Liberalism and the Model Minority Myth*

The last Japanese American internment camp officially closed in March 1946. However, the plight of the Issei and Nisei did not end. With the conclusion of internment, the JACL sought to rebound its reputation among the American public by focusing considerable attention on obtaining citizenship for its people. JACL leaders resolved to write about the Issei and their crucial contribution to the U.S. In 1948, the JACL

launched the Issei Story Project (ISP), which involved oral history interviews and the collection of important documents, photographs, and artifacts. As a final product, the JACL leaders hoped to form an accurate history of Japanese Americans, an examination of Nikkei–Japanese immigrants and their descendants in the U.S.–life experiences, and a widely-known account prepared for an unacquainted audience (Wu, 2014, pg. 150). With the project's chauvinism, JACL leaders underscored the project's global value considering America's involvement in another geopolitical conflict, the Cold War. "The recent 'setback in Japan' had reignited Asians' 'bad image' of the United States." And a narrative of Issei success in the U.S., particularly their resettlement to cities after internment, and a demonstration that "American democracy benefited all its people, including those of Asiatic ancestry," would elevate America's image (Wu, 2014, pg. 151). Thus, with the Cold War, the positive depictions developed more out of a geopolitical incentive to promote America's reputation after its damage during internment, than from a genuine admiration towards the resettlement efforts of Japanese Americans.

Assimilationists hold a paternalistic belief that a racial group is behaviorally or culturally, thus temporarily, inferior to whites and that they can be developed by instructing them on how they should act (KENDI, n.d.). They possess ideas that are "more subtle, seductive and coded" than those held by blatant racists. In this respect, the JACL, media, government, and other involved parties in the development of success narratives were all extensions of assimilationists in exploiting Japanese cultural values and success narratives to conform Japanese Americans to the world views and norms shared by the white American populace. Many assimilationists fail to be acutely aware of their internalized racism because "You can be someone who has no intention to be racist,' who believes in and fights for equality, 'but because you're conditioned in a world that is racist and a country that is structured in anti-black

[or of any other kind] racism, you yourself can perpetuate those ideas'" (O'Neal, 2017).

Ironically, the very belief, held by promoters of resettlement and assimilation, of Japanese Americans being the model for other minority groups, reveals that Japanese Americans were never societally accepted as "full Americans." Therefore, in considering the historical instance of Japanese Americans and the narratives that had spotlighted them, it is worth questioning, more broadly, whether assimilation has ever been, including the present, an achievable concept for marginalized groups in the U.S.

### *The Model Minority in the Japanese Agricultural Workers' Program*

The prevalence of racial liberalism in the U.S. during the Cold War era had not only involved Japanese Americans, but also Japanese nationals from mainland Japan who brought with them their aspirations of farming on U.S. soil. Given the possibility of the Bracero Program coming to an end, in the early 1950s, farmers in California were concerned over the looming labor shortage. To maintain a stable source for cheap and accessible labor, growers began to explore new mechanisms and ultimately arranged another program, the Japanese Agricultural Workers' Program (JAWP), in which Japanese farmers residing in mainland Japan would temporarily migrate to the U.S. as guest workers and work in fields owned by Californian growers.

On September 22, 1956, sixty-two Japanese men arrived at the Sacramento Municipal Airport, with the media characterizing them as model students to "grow into productive adulthood." Growers reported to journalists of the new guestworkers being abstinent and "fundamentally clean" as they kept their quarters "tidied up" (MIREYA, 2017, pg. 672). It is staggering to observe such stark contradictions between these comments and the nativistic portrayals of Japanese immigrants in the 1910s and 1920s in the West Coast. The Japanese, who were once described as being unsanitary, growing produce that spread disease, and living in squalid or inferior conditions than

their neighbors, were now heralded as young model students of minorities in the U.S.

Despite what they were promised, the reality was that once guestworkers arrived at their destination, they immediately faced a series of injustices. To account for their transportation costs and the JAWP's budget, Japanese workers were forced to subsidize money out of their own earnings to repay the cost for their travels to the U.S., leaving little to themselves.

Hearing about the labor conditions of Japanese guest workers, it was, once again, Japanese Americans, who questioned the positive illustrations of the JAWP and protested the JACL which endorsed the Program. The JACL patriotically claimed that welcoming Japanese guest workers would epitomize racial equality in the U.S. and that the Japanese guest workers would become "ambassadors of democracy that were so desperately needed following World War II and the U.S. occupation of Japan" (MIREYA, 2017, pg. 662).

In preserving the model minority image of Japanese guest workers, proponents of the JAWP not only argued for the political and diplomatic benefits of the JAWP, but also believed that the opposition to the JAWP was rooted in xenophobia. The multiple parties involved with the JAWP, from growers to the JACL, were so preoccupied with their own political and economic objectives in supporting or objecting to the JAWP that they failed to express genuine concern for the experiences and well-being of Japanese guest workers who had left their homeland to pursue the "American Dream" just as the first Japanese immigrants had done half-a-century earlier.

### *Larger DEI efforts involving AAPI students at RCDS*

In the same way that there are countless histories silenced by textbooks like Brinkley's, there are also diverse avenues to incorporate such relevant subjects in a school setting. I have identified five effective and distinct methods in which the RCDS community—and similar institutions—could accomplish this goal. Considering the

impracticalities of methods such as modifying the content in textbooks or the topics covered in the APUSH course, I have proposed multiple approaches that my school can choose from to navigate a polarized climate surrounding how history should be taught. The plans outlined below provide a range of learning opportunities for students and faculty in and outside of the classroom experience:

### *Interactive Notebook*

This notebook will be a Google Slides presentation containing, in each slide, a historical theme that is either missing or misrepresented in Brinkley's textbook. Each slide will have links to specific sections of this paper so that students will be able to select a specific segment of this paper to read. The notebook is designed to be accessible and engaging and will be shared with members of the AAPI club in the hopes that this tool will serve as one of many means to encourage AAPI students to learn more about each other's history.

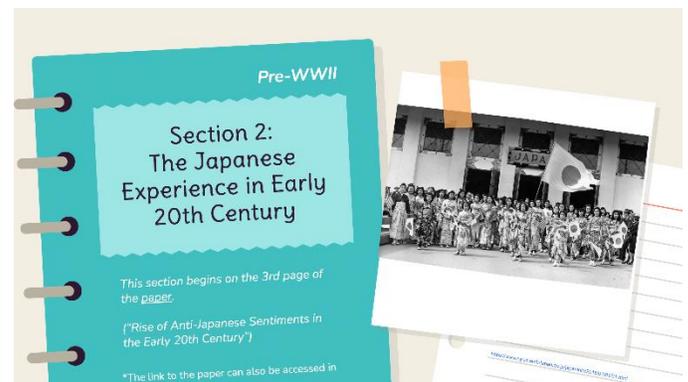


FIGURE 1: Representative slide from the Interactive Notebook

### *Underrepresented Groups in United States History*

Underrepresented Groups in U.S. History is an elective course offered at RCDS and is taught through focusing on historical figures representing various marginalized populations in the U.S. and their perspectives. This would be a great space to present my research and discuss

it with my peers. The Director of DEI, who also teaches the course, agrees with this idea and I will be able to collaborate with him to discuss how I could contribute to the making of the topics covered in the course.

*Reading Recommendation for Anti-Racist Books*  
These books—including the books that the school has already listed as optional community resources—can be added in the annual RCDS Summer Reading list to allow members of the community to further their knowledge. Books like *This Book Is Anti-Racist* by Tiffany Jewell, *Stamped from the Beginning* by Ibram X. Kendi, and *Start Here, Start Now* by Liz Kleinrock are all rich in history and anti-racist, anti-bias practices for teachers, students, and staff alike. These books can also be read by students through a Book Club with monthly meetings to discuss the relevant themes and ideas of each book.

*Utilizing community-wide communication tools and Advisory meetings*  
During the months celebrating and acknowledging the contributions of various marginalized groups in American history, students and faculty can select a figure belonging to any marginalized groups and explain what makes them special, an expansion of student and faculty efforts during the 2020-2021 school year. This information can be shared through daily postings on community-wide communication tools, such as RCDS News. Alternatively, one of the two cyclical Advisory meetings can be devoted for students and advisors in a House to take turns and share their findings within the House.

*Involvement of guest speakers*  
There are numerous nonprofit organizations working under a shared mission to ensure inclusivity, equality, and justice in society. For instance, Hollaback! offers programs to raise awareness about harassment and ways to combat them. Through inviting guest speakers of these organizations to the school during Community Meeting, students and faculty will gain

exposure to professional insights that they may not be able to obtain in a classroom setting. It is important to note that the RCDS community has been conscientiously supporting AAPI students. In alignment with these efforts, the action plans that I have identified come with the hope that through actively encouraging my school community to learn and refine our understanding of minority groups in the U.S., such individuals will be further uplifted, and that we will continue our work towards being an anti-racist, anti-bias space.

### **Final Words**

The ongoing Coronavirus pandemic has infected the country in many ways, exposing deep-seated hatred against the AAPI community in the U.S. The appearance of political figures, such as former President Donald Trump, bellowing discriminatory rhetoric to marginalize AAPIs within the country, and the alarming proliferation of anti-Asian bias incidents as byproducts of the pandemic unfortunately confirm the reality that inequality and injustice continue to affect AAPIs to this day. Moreover, a recent statistic indicates that the victims of violence after the outbreak of the pandemic has not been limited to a specific ethnicity: people of Chinese, Korean, Vietnamese, and other ethnic descent have been victims of violence (Center for the Study of Hate & Extremism, 2021, pg. 8). This data re-establishes the delusion which singularly characterizes AAPIs as "Asians," disregarding the diverse population that the term reflects.

In a generally chronological fashion, this paper explored the history of Japanese and Japanese American people in the United States from the early to mid-20th century, focusing on nativistic sentiments during the early 20th century, the developments of the model minority myth, and the experiences of guest workers in the JAWP program after the war.

However, as observed in the early portions of this paper, Alan Brinkley's *American History* fixates upon the treatment of Japanese Americans during World War II, particularly in the context of

internment, showing a general curricular disregard for this history. The action plans identified in the earlier sections of this paper take this actuality into consideration by outlining ways in which my school community can address the lack of historical representation of Japanese and Japanese Americans and, even broadly, foster awareness for the history of many other racial, ethnic, and marginalized groups.

The ongoing Coronavirus pandemic has infected the country in many ways, exposing deep-seated hatred against the AAPI community in the U.S. The appearance of political figures, such as former President Donald Trump, bellowing discriminatory rhetoric to marginalize AAPIs within the country, and the alarming proliferation of anti-Asian bias incidents as byproducts of the pandemic unfortunately confirm the reality that inequality and injustice continue to affect AAPIs to this day. Moreover, a recent statistic indicates that the victims of violence after the outbreak of the pandemic has not been limited to a specific ethnicity: people of Chinese, Korean, Vietnamese, and other ethnic descent have been victims of violence (Center for the Study of Hate & Extremism, 2021, pg. 8). This data re-establishes the delusion which singularly characterizes AAPIs as "Asians," disregarding the diverse population that the term reflects.

Despite these challenging circumstances, in July 2021, at a time when racial history and how it should be taught was under intense debate, Democratic Governor JB Pritzker of Illinois signed a bill mandating government-run schools to teach students about the contributions of Asian Americans in the economic, cultural, social, and political development of the United States. Pritzker commented, "It's a new standard that helps us understand one another" during a time when AAPIs are suffering from unfounded stereotypes and bigotry (BBC, 2021, par. 4). Such historic and contemporary stories inspire and give us hope for the future even during times of hardship while reminding us of the profound implications that America's past has to offer to the present.

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# Correlation of Race and Income with COVID-19 Vaccination Status in Monroe County, New York

Catherine Alexis  
The Harley School, USA  
cjca1917@gmail.com

## Abstract

Across the United States, there is a large disparity in vaccination rates for Black, Indigenous, and other People of Color (BIPOC) as well as for those living in poverty. A statistical analysis tests if these same trends apply in Monroe County, a county composed of Rural, Suburban, and Urban zip codes. It is found that the relationship between race and vaccination rate is direct-as the percent of White individuals increase, so does the vaccination rate of that particular zip code. It is also concluded that there is a correlation between high poverty rates and low vaccination rates. Among the multiple factors that lead to this conclusion, hesitancy and accessibility are focused on in this paper. Hesitancy, a leading cause of the lower vaccination rates for BIPOC is an issue that is produced from institutionalized racism in healthcare. For those in poverty, low vaccination rates are caused by insufficient access. Addressing these sources of low vaccination rates will not only benefit Monroe County but can be applied worldwide.

*Keywords: Vaccination, hesitancy, accessibility, race, poverty*

## Introduction

Despite eligibility, only 74.3% of adults in the United States have gotten at least one COVID-19 vaccine, according to the Center for Disease Control and Prevention (CDC). Vaccination rates for People of Color and those in poverty are even

lower (COVID-19 Vaccine Effectiveness, 2021). Hesitancy and access are two major causes of vaccination disparities addressed in this analysis. Hesitancy for people in America to receive COVID-19 vaccines stems from social, economic, and political factors. For Black, Indigenous, and other People of Color in the U.S.(BIPOC), systemic racism has been a major cause of lack of trust for the vaccine. BIPOC communities have especially been devastated by the COVID-19 pandemic. For example, Alaskan Natives have had 4 times the amount of COVID-19 deaths as their White counterparts (Quinn & Andrasik, 2021). Additionally, Black Americans have 2-3 times the amount of COVID-19 deaths as White Americans (Bogart et al, 2021). Medical history for BIPOCs in particular has been a part of mistrust, but it is necessary to acknowledge present-day racism in the field attributing to hesitancy (Bajaj & Stanford, 2021).

As stated by the CDC, Pfizer-BioNTech (12 and up), Moderna, and Johnson & Johnson's Janssen are vaccines currently authorized in the United States. High efficacy for these vaccines was studied through multiple clinical trials. Although the available vaccines are safe and effective, BIPOC communities are hesitant. Due to a lack of access, education, or mistrust within the healthcare system, there is a large gap for vaccinations between People of Color and White individuals (Quinn & Andrasik, 2021). For those in poverty, accessibility to get vaccines is lower than

TABLE 1. Excel data table of each zip code with percent vaccination rate, and demographics.

Zipcode	City	County	Vaccination Rate (8/1)	White	Black or AA	American Indian ar	Asian	Native Hawaiian an	Mixed	Hispanic a	Persons in Poverty
14614	Rochester	Monroe	31.90%	47.90%	39.80%	1.00%	3.10%	0.10%	4.40%	19.20%	31.30%
14420	Brockport	Monroe	47.40%	86.60%	5.80%	0.10%	3.20%	0.00%	3.20%	5.90%	25.70%
14464	Hamlin	Monroe	48.90%	96.50%	1.70%	0.00%	0.10%	0.00%	1.40%	1.40%	8.60%
14606	Gates-North	Monroe	51.40%	79.50%	11.50%	0.50%	4.20%	0.00%	2.90%	6.00%	7.20%
14609	Irondequoit	Monroe	53.40%	83.70%	10.00%	0.20%	1.30%	0.00%	2.50%	8.80%	8.30%
14445	East Roch	Monroe	59.70%	87.50%	5.70%	1.60%	0.60%	0.20%	3.90%	3.60%	11.90%
14623	Brighton	Monroe	60.50%	79.80%	6.20%	0.50%	10.20%	0.10%	2.50%	5.10%	9.20%
14514	North Chili	Monroe	61.70%	85%	9.60%	0.30%	1.70%	0.10%	2.70%	2.70%	7.20%
14468	Hilton	Monroe	62.80%	91.10%	7.50%	0.00%	0.00%	0.00%	1.00%	4.90%	13%
14626	Greece	Monroe	63.40%	84.60%	8.00%	0.20%	2.80%	0.00%	3.20%	6.10%	9.00%
14467	Henrietta	Monroe	65.30%	75.40%	10.60%	0.10%	9.60%	0.10%	2.70%	4.50%	14.70%
14506	Mendon	Monroe	65.50%	96.60%	1.30%	0.10%	0.80%	0.00%	1.10%	1.10%	7.30%
14580	Webster	Monroe	70.70%	91.90%	2.00%	0.10%	3.40%	0.00%	1.80%	2.90%	4.50%
14428	Churchville	Monroe	72.00%	97.40%	1.20%	0.00%	0.30%	0.00%	1.00%	1.20%	7.80%
14450	Fairport	Monroe	75.40%	97.50%	0.10%	0.70%	0.50%	0.00%	1.20%	5.30%	7.50%
14526	Penfield	Monroe	76.00%	91.80%	2.70%	0.10%	3.40%	0%	1.60%	3.60%	4.20%
14534	Pittsford	Monroe	79.60%	85.80%	1.70%	0.10%	8.70%	0.00%	3.10%	3.20%	3.30%

those of higher income. This is a factor that has historically created the vaccination rate gap between those with higher and lower incomes (Bedford et al, 2018).

I chose my county, Monroe County, New York to see if the same vaccination trends applied. Currently, Monroe County has a vaccination rate of 63.5%. Monroe County is comprised of both rural, suburban, and urban regions, unlike many counties in New York. According to the 2020 Census, out of a population of around 720,000 residents, approximately 30% live in The City of Rochester, 64% live in suburban neighborhoods, and 6% are from rural areas. Vaccination rates for various zip codes vary drastically. With the variety of residential areas in Monroe, the demographics of race and income also varies (United States Census Bureau, 2021).

**Objectives**

Find the correlation between vaccination rate and race for each Monroe County zip code as well as the correlation between vaccination rate and poverty.

**Hypothesis**

H<sub>1</sub>: As the percent of White individuals in a zip code increase, the vaccination rate will also increase.

H<sub>2</sub>: As the poverty rate increases in each zip code, the vaccination rate will decrease.

**Methodology**

For this study, data was collected for vaccination rates and zip code demographics. First, I collected vaccination rates from all Monroe County zip codes from the New York State COVID-19 vaccine tracker. I then collected race and income data from all Monroe County zip codes from the United States Census Bureau. For each zip code, I took data for percent race and percent in poverty. Out of the 43 zip codes that I found vaccination rates for, 17 had demographic data in the United States Census Bureau. Therefore, my statistical analysis used data from 17 Monroe County zip codes. For all of the statistical tests, SAS software was used. For both the race vs. vaccination rate test and the poverty vs. vaccination rate test, a Pearson correlation coefficient was found. Lastly, the measures of spread were also found using the three variables (vaccination rate, percent white, and poverty). All statistical tests were two-sided and a p-value of <0.05 was considered statistically significant.

## Results

First, the measures of spread were calculated. The majority of the vaccination rates that were collected were greater than 46%, mean = 61.5% ± 12.2%.

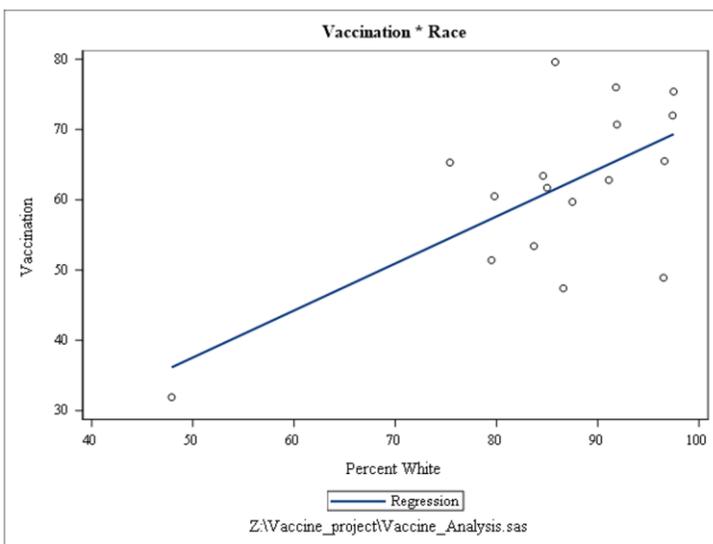
TABLE 1. Measures of spread for vaccination rate, percent white, and percent poverty.

Variable	N	Mean	Std Dev	Median	Min	Max
Vaccination	17	61.50588	12.16380	62.80000	31.90000	79.60000
Percent White	17	85.80000	11.81673	86.60000	47.90000	97.50000
Poverty	17	10.62941	8.30000	8.30000	3.30000	31.30000

To determine if there was a relationship between vaccination rate and race in Monroe County, a Pearson correlation coefficient was found. Vaccination rate and race in Monroe County were found to be significantly positively correlated,  $r(15) = 0.650$ ,  $p = 0.0047$ . As the percent of White individuals in a zip code increased, there was an increase in the vaccination rate.

TABLE 3. Measures of correlation for percent white and percent poverty.

Vaccination Rate and	Pearson Correlation Coefficient	p-value
% White	0.650	0.005
Poverty	-0.763	<0.001

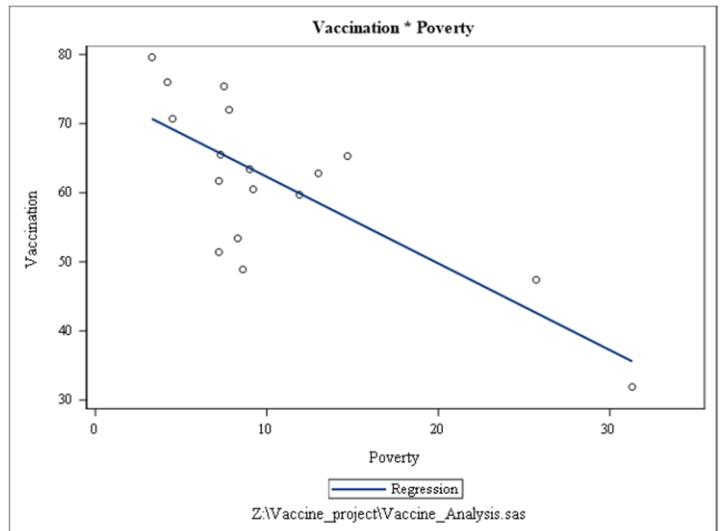


A Pearson test was calculated to show the correlation between the vaccination rate and the percent of individuals in poverty in Monroe County. Vaccination rate and poverty were found to be significantly negatively correlated,  $r(15) = -$

0.763,  $p = 0.0004$ . The data shows that as the poverty rate increased in a zip code, the vaccination rate decreased.

TABLE 3. Measures of correlation for percent white and percent poverty.

Vaccination Rate and	Pearson Correlation Coefficient	p-value
% White	0.650	0.005
Poverty	-0.763	<0.001



## Discussion

### *Vaccination Rate vs. Race*

The results of the Monroe County race vs. vaccination rate analysis are similar to vaccination disparities across the United States (Quinn & Andrasik, 2021). The data support my null hypothesis that as the percent of white individuals in a zip code increase, the vaccination rate will also increase. Concluded by the correlation coefficient of 0.650, it is evident that there is a significant correlation between race and vaccination rate. Due to previous trends in vaccination rates for People of Color, these findings were not surprising.

One logical reason concluding my findings is BIPOC vaccine hesitation, stemmed from mistrust. Not just COVID-19 vaccinations, but a history of minority vaccine hesitancy has been researched. For example, results for a study of the disparity in flu vaccination rates between White adults and Black adults were significant. Black adults were surveyed to have less knowledge about the vaccine, a greater amount of racial

consciousness, and lower trust in the flu vaccine. Furthermore, Black adults had a notably lower flu vaccination rate than White adults (Quinn et al, 2021). The lack of diversity in the medical system also creates a lack of trust within BIPOC communities. In a study led by Dr. Sandra C. Quinn, the impact of diversity was tested on the influenza vaccination. The study found that “perceived racial fairness” in the vaccination system created trust in the influenza vaccine. The perceived risk of side effects also increased with discrimination (Quinn & Andrasik, 2021).

Vaccination opportunities could be another factor explaining the varied data. For the flu season in 2009-2010, opportunities for getting vaccinated were observed in a study. Results indicated that there were significantly more “missed vaccination opportunities” (unvaccinated individuals who had a healthcare visit) for minorities than non-Hispanic Whites. Without equitable access to vaccines, there will be a gap in vaccination percentages (Maurer, Harris, & Uscher-Pines, 2014).

To increase COVID-19 vaccine intake for the BIPOC communities, both vaccine hesitation and opportunities need to be addressed. To make health institutions more trustworthy to BIPOC individuals, systemic racism needs to be eradicated. One feasible approach to this is for health care workers to engage with BIPOC communities more, and for providers to use motivational interviewing to address any mistrust (Gagneur, 2020). This process could include healthcare workers asking BIPOC communities about their needs to feel safe when it comes to healthcare, and what current policies are acting as obstacles to their confidence in the system, and later collecting and analyzing the results for future improvements. Another way to increase confidence in the vaccine is to let BIPOC physicians educate their communities. Racial identity can affect BIPOC’s response to receiving COVID-19 information. For example, Black patients had a more positive response to a video promoting COVID-19 precautions led by a Black physician than by a physician of another race (Bajaj & Stanford, 2021). To increase vaccine-

rollout efforts, race concordance could be a key component. Trust is one of the barriers to vaccination uptake in the BIPOC community, and by increasing the sense of security in the medical system, trust will ultimately increase (Kestenbaum, 2015).

To create more vaccination opportunities for BIPOC communities, routine healthcare visits need to be encouraged, and within those visits, vaccines should be highly recommended (Maurer, Harris, & Uscher-Pines, 2014). Although entirely eliminating systemic racism in healthcare is impractical, many steps can be taken to reduce its effects. By doing this, the rates for COVID-19 vaccinations for BIPOC zip codes can increase.

#### *Vaccination Rate vs. Poverty Rate*

The analysis also supported my null hypothesis that as the percent of individuals in poverty increases, the vaccination rate will decrease. These results are similar to those across the U.S. Research about vaccine accessibility for those living in poverty also shows lower rates of vaccinations, therefore these results are not surprising.

Although race also correlated with the vaccination rate, my analysis suggests that poverty has a stronger relationship. The results from my Monroe County analysis outcome are similar to that of previous vaccinations. For instance, a systematic review was done for human papillomavirus (HPV) vaccinations in 2014. From this analysis, it was found that 1% out of 118 million women in immunization programs were low-income (Bruni et al, 2016).

Many factors contribute to the historic inequity of accessible vaccines. Accessibility to the COVID-19 vaccines is the leading cause of the variation in the vaccination rates I analyzed. Struggling to get vaccination appointments is an example of the effects of inaccessibility for low-income individuals. Many COVID-19 vaccination centers are set up in areas that are hard to access due to variables such as transportation, work schedules, and disabilities. Additionally, online vaccine registration has disadvantaged those without

access to technology (Quinn & Andrasik, 2021). Addressing these factors will not only increase COVID-19 rates, but also for other vaccines (Lu, Gandhi, & Morgan, 2021).

One approach to increase vaccine accessibility is to go out to low-income communities for vaccinations. This way, transportation, and online registration issues are eliminated. Work schedules can also be better accommodated. Availability at large sites can also be slim, therefore vaccination outreach clinics will provide more opportunities (Lu, Gandhi, & Morgan, 2021).

### *Limitations*

A limitation of this study is from the data that I had collected from the New York State COVID-19 Vaccine Tracker, as the site does not gather data about age. The Pfizer-BioNTech vaccine is approved for people ages 12 and up only. Since the data does not take into account age, the true vaccination rates for eligibility aren't clear. Additional research could be done to only account for the ages that are eligible for the vaccine. For example, taking a census of only those who are vaccine-eligible and conducting the same statistical analysis.

Future research surrounding the impacts of BIPOC community engagement could be done to obtain knowledge about COVID-19 vaccine hesitancy. Surveying BIPOC communities about why they wish to not receive that vaccine could help. If Monroe County was able to collect data on why People of Color who have not yet received the vaccine are doubtful (through surveys and community outreach), reasons for hesitancy can be better addressed. These statistics would be able to tell us how to increase vaccination rates in Monroe County and eventually apply this across the United States. Two major hospitals in Monroe County, the University of Rochester, and Rochester Regional Health, have done work to reach those zip codes with lower vaccination rates. For example, Dr. Angela Branche, a Black physician at the University of Rochester, has increased the COVID-19 vaccine trial enrollment in the Black community using door-to-door

outreach. Along with Dr. Branche's community engagement, Sister Marsha Allen, a Black ordained minister in Rochester, has spread education to some of the poorest and predominantly POC neighborhoods in Monroe County using the same door-to-door approach (Steenhuysen, 2021). I have had the opportunity to help Sister Marsha Allen at a COVID-19 vaccination located in the City of Rochester clinic where vaccines are offered. The clinic has made an impact on zip codes that otherwise would have lower rates of vaccination. This work that improves the health of both BIPOC and low-income communities will be a factor in minimizing the COVID-19 pandemic.

### **Conclusions**

It is known that poverty and race are correlated to past vaccination trends in the United States. My analysis suggested that the trends apply to COVID-19 vaccinations in individual communities as well. To conclude, race and vaccination rate correlate, as well as poverty and vaccination rate. Multiple factors are causing these statistics. Vaccine hesitancy and accessibility not only affects my community, but all of the United States. It is important to address these variables to increase vaccination rates in BIPOC communities as well as low-income communities to reduce the longevity of the COVID-19 pandemic.

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# The psychosocial impacts of social isolation caused by public health strategies as a preventative measure of the spread of the COVID-19 on elderly adults: A systematic review

Zoe Atherton

British International School of Houston, United States

zoe\_atherton@houston.nae.school

## Abstract

The objective of this systematic review was to investigate the psychosocial impacts of social isolation caused by public health strategies as a preventative measure of the spread of the Coronavirus Disease 2019 on elderly adults. This research was conducted based on the mental health impact of previous pandemics including SARS and MERS, which showed significant effects, namely the increase in the suicide rate in Hong Kong during the SARS pandemic. The geriatric population was labeled as a “group at risk”, due to knowledge of previous public health crises as well as predisposing risk factors of increased age such as lower immunity and other affiliated comorbidities such as chronic pulmonary and cardiac conditions, diabetes, and hypertension, increasing the severity of SARS-CoV-2. Results have displayed that while being crucial to control the spread of the coronavirus 2019 disease, physical distancing and isolation measures taken by authorities internationally, especially focusing on groups at risk, can result in social isolation and loneliness. These primary psychosocial impacts cause serious secondary mental health impacts including depression, anxiety, and suicide. A distinct association between social isolation and loneliness with depressive symptoms was established, where being isolated and/or lonely displayed higher

depression scores. Loneliness, social disconnectedness and not wanting to be a burden to relatives were associated with the increase in suicide rates, as projected in the previous epidemic SARS in 2003. This paper calls upon the action of communities, and policymakers in assisting the coping of older adults to solve a worldwide problem that needs to be addressed.

*Keywords: COVID-19, Elderly, Quarantine, Social Isolation, Mental Health*

## Introduction

On the 11th of March 2020, the World Health Organization (WHO) announced the severe acute respiratory syndrome coronavirus 2 as a global pandemic, which originated from the Wuhan provinces of the People's Republic of China in December 2019 (Mackolil and Mackolil, 2020). Since being declared as a ‘public health emergency of international concern’, the pandemic has significantly impaired public health, economy, and the everyday life of billions. Although postulated to be less deadly than its precursors the severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS), SARS-CoV-2 is much more contagious (Banerjee, 2020). To prevent the spread of COVID-19, authorities all over the world imposed strict public health

measures, including the utilization of facial masks, rules of personal hygiene, maintenance of “physical distancing” of 6 feet and additional strategies such as suspension of all non-vital labor, lockdowns, and mandatory quarantine (Erden Aki, 2021).

However, the United Nations emphasized that, although the pandemic is a physical health crisis first, it has the potential to develop into a major mental health crisis as well, specifically for at-risk populations such as older adults. According to the CDC (2021), “mental health includes our emotional, psychological, and social well-being. It also helps determine how we handle stress, relate to others, and make healthy choices.” Though crucial to control the spread of the coronavirus 2019, physical distancing and isolation measures taken by authorities internationally, especially focusing on groups at risk, can result in social isolation and loneliness (De Pue et al., 2021). Studies that examined the physical vulnerability of the geriatric population concluded that predisposing risk factors of increased age and ageism such as lower immunity and other affiliated comorbidities such as chronic pulmonary and cardiac conditions, diabetes and hypertension increased the severity of SARS-CoV-2 and put them at a higher risk for fatality due to the virus (Mackolil and Mackolil, 2020).

Studies have proven that physical and social separation from those dearest to them, particularly during difficult times, may result in complicated grief and collective trauma reactions (Campbell, 2020). As older adults, especially those with preexisting medical condition are at a heightened risk, are subject to more mandatory quarantine and physical distancing measures, they have a higher potential for increased social isolation. Social isolation is commonly associated with poorer mental health outcomes and loneliness. (Campbell, 2020).

Among other things, worry and health-related fear mean the elderly are as susceptible to the virus as to its psycho-social impact. Subsequently, it is crucial to draw attention to the mental health of senior citizens to raise awareness of the need of

additional care and psychological support. In this systematic review, I will be introducing the different primary and secondary mental health impacts prompted by public health strategies to prevent the spread of the coronavirus 2019 and their associated risk factors in older adults.

## **Methods**

With the coronavirus pandemic recently taking the world by storm, related literature has been increasing rapidly. Although there are a multitude of resources available about covid-related populations at risk of mental health complications in the general population, few focus on the impacts of COVID-19 on mental health of the elderly population and most studies were conducted either in the very early stages of the pandemic when social distancing was recommended but lockdown was not yet instated, or lockdown was in its early stages. Only a scarce number of studies mention the pandemic’s secondary mental health impacts, particularly suicide, on the geriatric population, however, often included a meta-analysis of groups at risk and so lacked sufficient focus on qualitative results.

A systematic review was conducted with the aim of identifying primary and secondary mental health impacts of public health measures to prevent the spread of COVID-19. An analysis of search results was led using PubMed to access articles that matched the preestablished set of search terms: COVID-19, senior citizens, and mental health. Studies with a focus on COVID-19 patients and the mental health effect of being sick with the coronavirus were excluded because the research question assessed specifically the impacts of public health measures due to COVID-19. Papers that concentrated on the mental health of healthcare workers were excluded, as they were not put through the same public health measures as the general elderly public and often exposed to additional psychological stress, which may impact the validity of my results. Research that involved specific secondary mental health impacts related to COVID-19 such as depression,

anxiety and suicide were included if enough qualitative data was available. After each stage of analysis, Zotero was used to organize included studies, which were removed if found irrelevant to the study.

To assess the quality of the articles, three phases of analysis were performed resulting in the exclusion of articles.

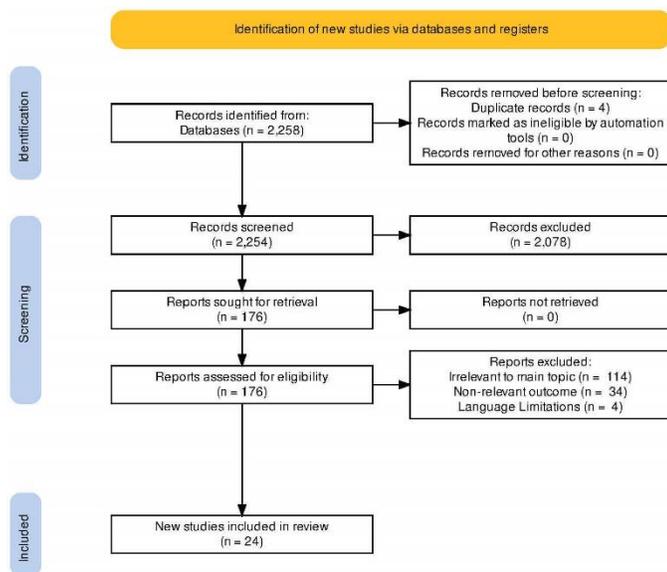


FIGURE 1: PRISMA flow diagram detailing the search and selection process of 2,258 records evaluated in this systematic review.

First the title of 2,258 articles was scanned and those that were irrelevant to the main topic were excluded. Irrelevance was established if the title did not include the predetermined set of keywords: COVID-19, senior citizens, and mental health. Additionally, 4 duplicate records were identified and removed automatically by the Zotero extension. Next, the abstract of the remaining articles was surveyed and those that had a non-relevant outcome or were irrelevant to the topic of the research question were excluded, leaving 176 papers. Finally, a full-text scan was performed, inspecting the quality and validity of the article, by referencing the number of citations and the format of the paper. There were three main reasons why papers were excluded in the

full-text scan. Firstly, 114 studies were excluded because the results were irrelevant to the main topic, most referring to groups at risk for mental health complications due to COVID-19, instead of its impacts on the geriatric population. A further 34 papers were excluded as they had a non-relevant outcome, often focusing on quantitative rather than qualitative data, and being conducted earlier in the pandemic where the correlation between the impacts of COVID-19 public health measures and mental health were weak. The last 4 studies were excluded, due to language limitations, two of which written in Chinese with poor translation, one written in German and the last in Japanese. Research papers that lacked quality were finally excluded, leaving the 24 studies included in the systematic review.

## Results

### *Primary impacts: Social isolation and loneliness*

For older adults who live alone more often than younger individuals (Müller et al., 2021), the arrival of dear ones, such as friends and family, are a significant source of social interaction and delight. However, social distancing measures imposed upon them due to COVID-19, mean the geriatric population is confined within their homes and have limited contact to the outside world (Mackolil and Mackolil, 2020). This lack of social interaction may cause a large majority of the geriatric population to feel lonely, as they may have lost their significant other to old age and must now also limit contact to family to protect themselves. As elderly individuals already suffered with social isolation and loneliness in the absence of the pandemic, this resulted in a surge of social isolation among older adults paired with intensified worry about the health of family members and friends, as well as their own (Erden Aki, 2021). Loneliness can be defined as “the subject feeling of being alone, while social isolation describes and objective state of individuals’ social environments and interactional patterns” (Hwang et al., 2020). Social isolation can have damaging effects on the elderly and studies have shown a strong relationship between

“social isolation and loneliness with increased mortality, decreased functioning, increased risk of Alzheimer’s disease” (Müller et al., 2021), as well as depression and suicidal attempts (Erden Aki, 2021). The impacts of social isolation and linked loneliness are especially damaging in the geriatric population due to their increased dependence on others. Many individuals in the elderly population require servants or other family member for their daily functioning and may rely on medication, housekeeping or have specific dietary needs. As a result of the containment laws, servants have stopped providing services and relatives are no longer allowed to visit them to protect their physical health. This in turn has led to a reduction in their quality of life with many older adults overstrained by the lack of necessitated help, leaving older adults helpless and lonely (Mackolil and Mackolil, 2020).

Additionally, further loneliness and isolation is caused by the geriatric population’s lack of technological expertise. In times of constrained travel, online platforms offer an alternative to stay connected with loved ones and meet the need to socialize. Due to most elderly individual’s lack of skill with using technology, they may not be able to use technology to reach out to family, friends, and other members of the community, placing them at a disadvantage as their social needs are not met (Mackolil and Mackolil, 2020). It also means they may have difficulties accessing online services such as religious or spiritual services, home-delivery services, medical assistance, and virtual therapy session (Mackolil and Mackolil, 2020), leaving the geriatric population with a limited use of services and requirements. Moreover, their inexperience with technology may expose them to ill-information and fake news because they may be unable to check the authenticity of new sources, placing them at a higher risk of experiencing symptoms such as fear, health anxiety, and loss of hope. These coupled with their inability to use social media as a tool may result in boredom and loneliness and may develop further into even more damaging mental health consequences.

However, the impact of loneliness caused by social isolation due to COVID-19, is not to be underestimated. Loneliness is associated with a general decrease in wellbeing of a person and can lead to various physical and mental repercussions, including elevated systolic blood pressure as well as an increased risk for cardiac disease (Hwang et al., 2020). A combination of loneliness and social isolation have also been affiliated with an increased risk for coronary artery disease-associated death, despite having no prior history of heart attacks (Hwang et al., 2020). This poses another significant risk, especially for older adults, who may already be facing various physical health issues associated with age being an independent risk factor for a higher rate of all-cause mortality (Hwang et al., 2020). Being lonely also provokes adverse impacts on mental health including reduced time in bed spent asleep with a 7% reduction in sleep efficiency and increased wake times (Hwang et al., 2020). While loneliness may cause adverse health impacts such as physiological stress responses, social isolation is more closely associated with changes in behavior. Behavioral changes observed due to social isolation include the adoption of an unhealthy lifestyle such as smoking, substance use, decreased levels of physical activity and non-compliance with medical prescriptions (Hwang et al., 2020). Especially the latter could lead to fatal consequences for the geriatric population, especially for those affected by dementia and Alzheimer’s disease.

#### *Secondary impacts: Depression and anxiety*

The onset of a new pandemic is fear-inducing, especially for older people who are considered at higher risk of for the virus. Confinement and mandated isolation, while necessary to prevent the spread of COVID-19 may cause experiences such as depressive symptoms, pessimism, deteriorations in cognition, and disruption in sleeping patterns, which is, according to Buenaventura et al. (2020), “consistent with known psychological reaction of stress, anxiety loneliness, and agitation in a

pandemic.” Depression is defined as “a common and serious medical illness that negatively affects how you feel, the way you think and how you act,” by the American Psychiatric Association (2021). Since the outbreak of COVID-19, 37.1 % of elderly in China displayed symptoms of depression and anxiety (Buenaventura et al., 2020). Postulated causes of these symptoms include the disruption of daily activities for the geriatric population, which can pose a negative impact on older individual’s cognitive impairment, leading to poorer mental health, namely anxiety and depression.

Loneliness and social isolation, which are direct results of the infection control measures, particularly lockdowns, have a consistent relationship with depressive symptoms. A study conducted by Müller et al (2021) presented distinctive results of a clear association between social isolation and loneliness with depressive symptoms, where being not isolated and lonely and being isolated and lonely both displayed higher depression scores. While older individuals were less likely to suffer adverse mental health outcomes than younger individuals under normal circumstances due to their resilience, their increased risk of social isolation and loneliness without the prospect of direct contact due to the restriction imposed on them, means they are more vulnerable than ever. People being treated for conditions concerning mental health prior to COVID-19, were particularly prone to fear, anxiety, and depression with levels increasing so far, they sometimes surpassed the initial complaints, deepened by greater loneliness caused by social isolation measures, reporting that the more distant social relationships throughout the pandemic, the higher the depression levels (Tyler et al., 2021). Similarly, self-perceived disconnectedness from family, friends, and the community has resulted in heightened anxiety and depressive symptoms (Mukhtar, 2020).

### *Secondary impact: Suicide*

The long-term restrictions applied to elderly people (aged above 70) in the form of quarantine and lockdowns have resulted in serious mental health consequences, above all suicidal feelings. The number of calls from older people to call centers, where people call if they have suicidal feelings, has reported an increase of 60% with a large proportion of the rise accounted for by the geriatric population (Skoog, 2020). The reason for this significant increase lies with the social isolation senior citizens have experienced, because of the lack of social contact with relatives, friends, and the community. This surge in suicidal feelings has led to a significant increase in suicide rates in the elderly population (Shuja et al., 2020), which may have been amplified by their lack of technological expertise (mentioned earlier), as most of the members of the geriatric population may be unable to reach out to call centers and may not want to burden their family (Wand et al., 2020).

The geriatric population is especially prone to the adverse effects of isolation, namely suicide, as living alone, social isolation and loneliness are well-known to increase the risk of suicide in later life (Wand et al., 2020). Even before public health measures such as quarantine exacerbated loneliness and social isolation leading to suicide, according to WHO, the elderly had higher rates of suicide than the general population (Sheffler et al., 2020). The Interpersonal Theory of Suicide (IPTS) explains why individuals engage in suicidal behavior, posing that capability to commit suicide is to be differentiated from the desire to engage in suicidal behaviors. Thwarted belongingness and perceived burdensomeness make up the desire for suicide, while genetics, habituation when repeatedly faced with painful or fear-inducing scenarios, and lived experiences may influence capability (Sheffler et al., 2020). Strict social distancing measures mandated for older adults, leading to social isolation and ethical treatment guidelines of COVID-19 are thought to increase the desire for suicide by cultivating thwarted belongingness and perceived burdensomeness.

According to Sheffler et al. (2020), thwarted belongingness includes the absence of reciprocal care and loneliness. Public health measures are disrupting the already smaller networks of the geriatric population, by confining them to their homes, increasing social isolation. Social isolation linked to social distancing policies might distress psychological functioning and late-life health, aggravating the existing risks for suicide. Similarly, the absence of positive social relationships and loneliness among older adults provide substantial risk factors when concerning morbidity, mortality, and suicide (Sheffler et al., 2020).

“Perceived burdensomeness is the belief that one is a burden on other or on society” (Sheffler et al., 2020). Perceived burdensomeness is especially prone in older adults during the coronavirus 19 pandemic, due to the fear of becoming infected and then being a burden to their families or infecting other family members (Rana, 2020). This is proven by the SARS epidemic in 2003, as causes of suicide among adults aged 65 and older, related to the fear of becoming infected and then being a burden to relatives. Further proof is available when concerning the situation in India currently, with 80 of the 300 non-coronavirus deaths reported during the lockdown caused by the fear of being infected or loneliness (Rana, 2020). Additionally, articles published during the pandemic that discuss the ethical decision of intensive care specialists of denying life-saving care to those most heavily affected, usually older people, with age being one of the main criteria to deny services, send the elderly the message, that they are a burden on society. The medical consensus of saving those with more years left, portrays the geriatric population as expendable, which may cause them to develop perceptions of being a burden to a society better off without them (Sheffler et al., 2020).

To establish the extent of the suicide risk associated with COVID-19 and its implications, drawing on previous public health crises, such as SARS is beneficial. The 2003 severe acute

respiratory syndrome (SARS) epidemic exhibited detrimental mental health effects in older adults. In Hong Kong, the suicide rate after the SARS epidemic skyrocketed from a previous suicide rate of 28.4 per 100,000 in 2002 to a suicide rate of 40.4 per 100,000 in 2003 (Chong et al., 2020). Deductions for what aspect of the epidemic this may have resulted from included loneliness and disconnectedness, (Chong et al., 2020) as well as fear of getting infected, anxiety over social isolation and not wanting to be a burden to relatives (Erden Aki, 2020). The association between increased suicide risk and loneliness has been proven by multiple studies, determining an association between loneliness and both suicide attempts and completed suicide (Hwang et al., 2020). The suicidal incidences of among specifically elderly adults in Hong Kong following the SARS epidemic, rose by 31%, being especially prone in elderly women, postulated to be because of difficulties in gaining access to social support and healthcare services, due to a lack of technological expertise (Erden Aki, 2020). This provides a justified prediction of the extent of the detrimental impact, COVID-19 may have on suicides in the elderly population.

## Discussion

In this systematic review, the psychosocial impacts of social isolation caused by public health strategies to prevent the spread of the coronavirus 2019 pandemic were evaluated. Overall, the geriatric population faced social isolation effectuated by the mandated public health measures such as lockdowns to prevent the spread of the coronavirus 2019. This caused a multitude of adverse secondary effects chiefly loneliness, depression, anxiety, and suicide due to a lack of social interaction and communication driven by both the lack of social contact with friends and family due to public health measures and their lack of technological expertise. The mental and physical health impact of social isolation and loneliness should not be underestimated, providing potentially fatal

consequences for the geriatric population, its primary impacts resulting in suicide.

Limitations to my findings included the recent appearance of the coronavirus 2019 pandemic, meaning in most cases researchers could only predict or suggest the long-term impact of the isolation methods associated with the virus. Additionally, many of the studies included in this research paper were released when lockdown was still in its early stages, meaning the full extent of the long-lasting quarantine measures were not considered. It is also important to note, that inclusion and exclusion criteria and its application may have been biased, as a certain outcome was preferred. Studies that contradicted the preferred outcome of the research question were excluded, so certain factors such as the increased resilience of the geriatric population were not considered.

This systematic review has highlighted the detrimental effect that the coronavirus pandemic has had and will have on elderly individuals. Therefore, it is crucial to provide coping mechanisms, as this may lessen the long-term impact of the pandemic on the mental health of older adults. Some positive coping strategies that may assist older adults in staying resilient, include walking outdoors, breathing exercise, adjusted daily routines, and keeping socially connected with friends and family (Finlay et al., 2021). Communities should support elderly individuals by creating social infrastructure for mutual support and transmission reduction (Finlay et al., 2021). Grocery stores could, for example, introduce special shopping hours for older and at-risk populations or communities could organize mutual-aid groups that deliver groceries, medications, and other essential supplies needed by vulnerable population. Policymakers should strengthen infrastructure to allow for vulnerable populations to have access to essential resources, services, and reliable public health messaging. Investments in areas such as neighborhood infrastructure may encourage regular physical activity, which benefits mental and physical health and promote social cohesion

(Finlay et al., 2021). Adopting these steps may help the geriatric population to keep social connections with family and the community, maintain healthy activities and control their emotions and psychiatric symptoms, leading to a possible relief in the adverse consequences of loneliness and isolation (Hwang et al., 2021).

The mental health of elderly individuals worldwide needs to be addressed and acting now is crucial to be able to aid them during the post-pandemic period. Further research should be invested in developing virtual health care (advancing telehealth), new technology to solve issues addressed in this systematic review and changing government policies to include and consult members of the geriatric population in future decisions.

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# Impact of Weight Stigma on Obese Women and Their Reproductive Health

Fatima Bagom

Stuyvesant High School, United States

jonwun123@gmail.com

## Abstract

The obesity epidemic continues to grow globally, with many health and global administrators stunned about how to approach it. The health care system sticks to an individualistic approach, where responsibility and shame are placed on the individual and not big food companies or global shift to sedentary lifestyles. The roots of weight stigma center around shaming and discriminating against individuals based on their weight. The principles of weight stigma and weight bias find their ways in health care settings, including the OB GYN field, creating life-threatening situations. However, the connection between weight stigma in reproductive care and obese women remains heavily under-researched. This prompted an opportunity for a systematic literature review to unfold the health disparities obese women face in reproductive care. Four academic databases were used to locate over 4,000 sources. Sixteen of these papers were used in the final systematic review. Two main themes were expressed through the review: (1) Impacts of Weight Stigma and (2) Approaches to Weight Stigma. Recommendations for further interventions include increasing research on the topic and empowering obese women within clinical settings.

*Keywords: Weight stigma, obesity, women, reproductive care, quality of care*

## Introduction

### *Overview*

The obesity epidemic has consumed America and many western countries over the last couple of decades. Obesity has become a global epidemic, dominating countries all over the world. The reasons behind the epidemic come down to the increase of the manufactured food market (along with certain food marketing practices) and an institutional shift to less physical activity among individuals. However, the individual is the one to pay. Not only do health complications often come along with obesity, so does the blame; a survey conducted by economists revealed that most people believe individuals are to blame for their own obesity (ACES, 2014).

Adding on to the list of challenges obese people face is weight stigma. Weight stigma is the fourth most common form of discrimination in the United States, and it has an array of consequences (Mulherin et al., 2013). Stigma refers to an exhibition of attitudes or discriminatory actions towards a person deemed to be inferior or disliked. Weight stigma is a result of weight bias — the bias against overweight and obese individuals — which works hand in hand to devalue obese individuals. There is abundant evidence suggesting that obesity causes feelings of disgust, anger, and dislike in others (Phelan, 2015). Unfortunately, this stigma is prevalent just about everywhere, including within the healthcare system. This attitude (whether it is conscious or not) affects many, if not all, overweight and obese individuals. Stigma in healthcare settings can

cause adverse health and psychological harm to the receiver of the stigma. One field is particularly vulnerable to weight stigma: women's reproductive health.

#### *Weight stigma faced by nonpregnant women*

Women more often than men will face weight stigma. Whether it be social media, models on runways, or from family and friends, women are constantly reminded that they "need" to look a certain way. Women's weight and bodies are a constant topic of discussion from a very young age. When girls visit a physician's office, they are reminded of their weight and told to maintain their physical appearance (even if they are overweight in the slightest). Women tend to be face weight stigma at higher rates than men, even at lower levels of excess weight. "For example, men tend to report considerable stigmatization at a Body Mass Index (BMI) of 35 or higher, whereas women report experiencing notable increases in weight discrimination at a lower BMI of only 27" (Weight Bias, 2017). For overweight and obese women, practically all their problems are pinpointed to their weight. In particular, issues with their reproductive organs can be overlooked or misdiagnosed due to their weight.

#### *Weight stigma faced by pregnant women*

Weight stigma is a universal occurrence and unfortunately, it is directed at pregnant and postpartum women as well. Pregnancy is a special case in the sense that there are two types of weight stigma: one directed towards women who gain weight during pregnancy and the other towards women who were obese before their pregnancy. This review will mostly focus on the latter and keep its focus on obese individuals' experience through healthcare but there are some overlaps.

The occurrence of weight stigma in obstetrics is under-researched, yet the risks of being obese during pregnancy and how ways to manage it have steadily increased in literature. This gap adds to the weight stigma and further strengthens it. Yet, social media continues to portray "baby

weight" in a demonizing way. It continues to push for ideal pregnant bodies and pressure individuals to "bounce back" from their pregnancy bodies (Nippert et al., 2021). The prenatal and postnatal time for women makes them vulnerable to a variety of mental health issues, and the projection of weight stigma on them is concerning. The state of the child-bearing individuals is crucial for their well-being and their offspring.

#### **Methodology**

A systematic literature review was performed. This aims to identify, evaluate, and summarize findings on a specific issue (Gopalakrishnan & Ganeshkumar, 2013). Numerous academic databases and research sources were used to gather relevant papers. The academic databases include ProQuest, Science Direct, Gale Health Reference Center Academic, and Google Scholar. Science research sources include PubMed, Open Science Directory, and Science Daily. Keywords were used to search for papers and all papers used were in English.

The keywords used were "women," "weight stigma," and "OB GYN." Variations of the search terms were also used, such as replacing "OB GYN" for "pregnancy" or "reproductive health", to broaden the search. Upon entering such terms into the databases, (n=4,000) results were yielded and (n=89) papers were read. The other articles were not viewed due to how expansive the results were and complete irrelevancy of the title to the topic. From the papers that were read, (n=54) were excluded due to irrelevancy. Most focused on a topic completely unrelated to the three main terms or were focused on battling obesity rather than weight stigma. Additional papers (n=15) were excluded due to inaccessibility to full texts and (n=4) were excluded due to being written in languages other than English. All papers were organized in a Google Spreadsheet and were reviewed from there.

Sixteen sources are included in this review. All sources used were obtained from credible databases, peer-reviewed journals, accredited

institutions, and national agencies' websites. The data used in this review is reliable. Figure 1 demonstrates the methodology used.

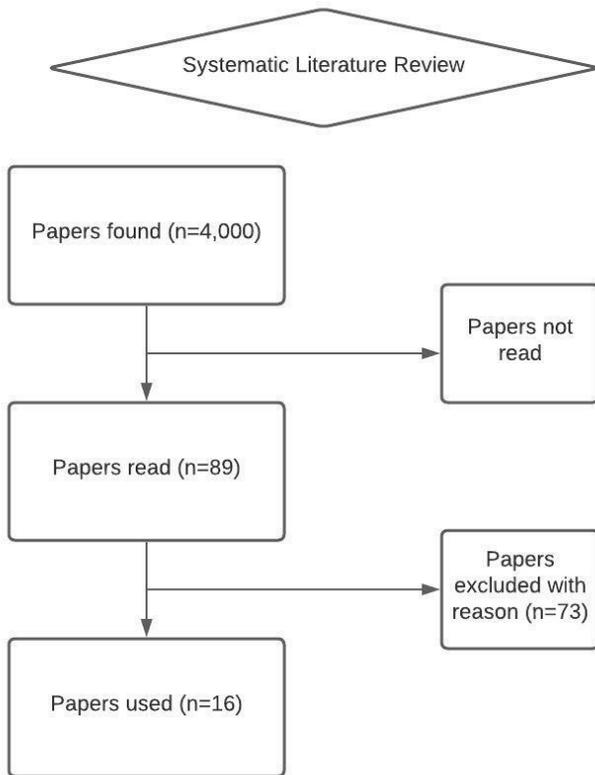


FIGURE 1: Visualizes the methods used for this systematic review.

## Impacts of Stigma

### *Reduced care*

Physicians and other healthcare workers play a vital role in the health of people. They help to make sure their patients are in healthy states of being and provide screenings to detect any signs of illness. Their job is to identify issues and formulate plans to help patients battle (and even cure) said issues. Sadly, weight stigma can create boundaries of care for obese people.

The negative attitudes underlying enacted stigma reduce the quality — and even the quantity — of patient-centered care. Providers' attitudes about a patient's weight can reduce the quality of the encounter and the patient's satisfaction (Phelan, 2015). At many times, patients' problems are

completely overlooked. Researchers from Texas carried out in-depth interviews with women on this issue. An interviewee named Lynette was refused treatment for her arthritis by a chiropractor because of her weight. She stated that he “took one look at me and said 'All you need to do is lose weight and that would solve all your problems'... He didn't bother with X-rays or an examination or anything” (Blackwell, 2008). In a study of over 300 subjects, obese patients were 1.65 times more likely than non-obese individuals to have undiagnosed medical conditions, indicating that misdiagnoses occur (Fat shaming in doctor's office, 2017). Many more instances occur throughout the world, but this issue is not spoken about in media.

### *Lack of cancer screening*

A field where there is more awareness is cancer screening. Cancer is a group of diseases characterized by abnormal cell growth that has the potential to spread throughout the body. Cancer is one of the leading causes of death worldwide and has had lots of attention on it over the years. It is often talked about in school; by an early age, the importance of cancer screening and prevention is discussed. However, obese women are significantly less likely than their non-obese counterparts to have gynecological and breast cancer screenings (Lee & Pausé, 2016). Many studies showed that mammogram use greatly decreased amongst women with higher body mass index (BMI) (Mensing et al., 2018). Though obesity is one of the risk factors of breast cancer, obese women do not get proper and regular screenings to help detect cancer early on. In addition, obese women with breast and cervical cancers are more likely to die from breast and cervical cancer than non-obese women with these cancers, yet access to screenings remains low (Lee & Pausé, 2016).

### *Isolation from healthcare*

Oftentimes, weight stigma results in avoidance of clinical care if patients feel as though their weight will be a source of stress or embarrassment. In the

case of cancer screenings, many obese women avoid the clinical setting in fear of embarrassment, lack of appropriately sized examination equipment, and poor communication between the patient and the provider (Aldrich & Hackley, 2010).

Lack of proper communication due to stigma along with ignorance towards patients' issues leads to mistrust in the providers. Enacted stigma can reduce the probability that the patient will comply with the provider or even return (Aldrich & Hackley, 2010). Stigma in the clinical settings leads many women to feel like a burden, and in turn, avoid getting clinical care. Women in a Texas study stated that healthcare professionals didn't see them as normal people with a condition, but rather as overweight women who needed their help (Blackwell, 2008).

The long-term effect of avoidance and postponement of clinical care is that obese individuals may develop more advanced and more difficult to treat conditions.

#### *Long term physiological and psychological effects*

The effects of weight stigma have lingering long-term effects. The most common effect is the retention and even gaining, of the weight of individuals who face weight stigma. In many studies, when participants are manipulated to experience weight stigma, their eating increases, their self-regulation decreases, and their cortisol (a stress hormone) levels are higher relative to controls (who are not exposed to weight stigma), particularly among those who are or perceive themselves to be overweight (Tomiya et al., 2018). Weight stigma experienced by pregnant and postpartum women is associated with more gestational weight gain and postpartum weight retention (Incollingo et al., 2020). The stigma associated with weight ends up being the driving force of the obesity epidemic. As more people perceive stigma for their weight and see themselves as overweight, the more their health declines. The mere perception of oneself as being obese is associated with biological markers of poorer health, including unhealthy blood

pressure, HDL cholesterol, triglycerides, and glucose levels (Tomiya et al., 2018).

Research shows that weight stigma leads to psychological stress, which in turn can lead to poor physical and psychological health outcomes. Women in the US were surveyed about weight stigma during and after pregnancy. Data revealed that they experienced more depressive symptoms, harmful dieting habits, and stress when discussing pre-pregnancy BMI (Incollingo et al., 2019). Furthermore, patients with obesity who experience stigma may experience a high level of stress which can contribute to impaired cognitive function and ability to effectively communicate. (Aldrich & Hackley, 2010).

### **Intersectionalities within Weight Stigma**

#### *Race*

Though it is acknowledged that women face weight stigma in OB GYN and other health fields in term of care, the effect of the race of the women is less understood. Studies show that Black women have a higher risk of obesity than White women, but "despite higher body mass, research suggests that Black women are more satisfied with their bodies than White women" (Chithambo & Huey, 2013). The perception of their own bodies goes beyond just being satisfied or not – it effects the way they cope. A study involving 2,378 America adults (with 50 percent women) had some valuable findings. " Compared to white women, Hispanic women were more likely to cope with stigma by engaging in disordered eating behavior (e.g., bingeing, starving, or purging), whereas black women were less likely to cope by engaging in disordered eating behavior" (Race and Gender, 2017). Unhealthy coping often puts individuals back on the cycle of shame and weight gain. There is a disparity in which women are more at risk for health problems related to weight stigma depending on their race, interconnecting the two. As Himmelstein states, "Failure to meaningfully examine racial identity means missing important and unique experiences which contribute to obesity-related health disparities" (Race and Gender, 2017).

## Discussion and Conclusion

Weight stigma affects all populations and in all settings. In particular, it proves to be an obstacle for women, who regardless of their BMI, face weight stigma. A woman's weight and body are always a topic of discussion and have created years of shame for those who do not fit the perfect model. However, the effect of this stigma surrounding weight goes beyond a societal expectation - it becomes a barrier for women to proper care. Pregnant or not, overweight and obese women face discrimination in reproductive care. Health professionals' negative attitudes regarding a patient's weight can limit the quality and quantity of the patient's care. Many physicians often overlook the patient's concern and blame all issues on weight while others make remarks about weight. All this and more lead obese women to feel like a burden or embarrassed, resulting in less frequent visits, a more negative outlook on their weight, and mistrust in healthcare providers. This in turn can cause an array of issues, ranging from lower cancer screening rates to many ailments and mental disorders. It is imperative to address the inequality of care for overweight and obese women.

### *Limitations*

Limitations of the ideas presented root from the lack of research on this particular topic. Out of the thousands of papers yielded from the search terms, only a handful discussed the health barrier for obese women in reproductive care. Interestingly, many of the papers were authored by the same two authors.

Additionally, the data in many of the studies do not encompass all obese women's experiences. All the studies with empirical data (that were screened for this review) were based in Western countries. Many countries and regions outside of this selection were not accounted for. Furthermore, much of the literature regarding obese women came from surveys or thorough interviews, creating a potential for bias.

### *Recommendations for Further Research*

Further research is crucial to making improvements towards the care obese women receive, especially towards their reproductive health. Most research focuses on obese individuals in general and a few focus on pregnant obese women, but very few bases around just obese women. It is widely known that obese women face discrimination regarding reproductive health but there have not been many studies conducted. Further research should center around obese women's barrier of care in reproductive health. In addition, discrimination in health care settings occurs due to weight and gender, but it also occurs due to race. Researchers should further delve into the inequalities obese women of color face (Ferrante, 2016). There needs to be abundant and credible research in order to stop discrimination based on weight.

### *Recommendations for Future Interventions*

Future interventions should keep both weight bias and gender into consideration. Women are often left out of male-oriented healthcare and obese people are left out from a lower BMI-oriented definition of "healthy." Future interventions should focus on empowering obese women so that they can continue to visit clinical settings without fear of embarrassment or stress. Health care settings should be a comfortable place for obese women to speak of their health issues. A suggestion by some researchers is to adjust terminology. Although traditional terminology is still in place in health care settings, the effect of revising terminology used for obese women has potential. Studies found that women specifically disliked the usage of terms such as "obesity," "BMI," and "people your size," in healthcare settings. Among weight-related words, the word "weight" was ranked the highest and the word "obesity" was ranked the lowest (Hurst et al., 2021).

There should also be stricter laws regarding discrimination in a clinical setting between providers and patients. Providers should make it

their priority to make their office a comfortable and open place. Regarding the disparity of cancer screenings, there should be a push to get more obese women in the office and screened. Raising awareness on such cancers and the vital role screenings play in prevention can aid with this. Finally, there needs to be more diversity in the healthcare field. When everyone is represented, better initiatives and plans for care can be formulated.

### *Necessity for Interventions*

Intervention is key for more obese women to get the proper care they need. Without intervention, more and more women will avoid their needed clinical visits, lack proper reproductive care, and swindle into a hole full of physical and mental ailments, all that could have been prevented.

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# Evaluation of rgGH Therapy in Treating Small Stature as a Result of Being Born Small for Gestational Age (SGA) Without Catch-up Growth

Ralph Ballard

The Latymer School, United Kingdom  
ralph.ballard04@outlook.com

## Abstract

Being born small for gestational age (SGA) refers to being born with a birth weight under two standard deviations for the gestational age and sex of the population. 10% of children born SGA will not experience catch-growth and, if left untreated, this can result in a lower health-related quality of life. Recombinant growth hormone (rhGH) therapy is a common treatment that aims to increase the height velocity of children suffering from short stature. Although many studies have been carried out into the use of rhGH in treating short stature, few have focused solely on its effect on children born SGA. This literature review analysed sources from three databases (n=634) and evaluated the safety, effectiveness and outcomes of rhGH therapy in treating children born SGA. The main conclusions reached were that SGA children usually react well to treatment with a +1.03 SDS change over the first two years, but that the overall outcome will be affected by a number of factors. The treatment was deemed cost-effective for the change in quality of life. Although most side effects were positive - including improved lipid profile, lean mass and Performat IQ - not enough data was present to come to a clear conclusion on metabolism, while the treatment led to an over-correction of insulin sensitivity resulting in subjects being at greater risk of Type 2 diabetes. There was a lack of data on long-term effects. Overall, it appears rhGH is effective in treating children of short stature born SGA without catch-up growth.

*Keywords: SGA, rhGH, short stature*

## Introduction

Small for gestational age (SGA) refers to a child with a birth weight under two standard deviations for the gestational age and sex of the population (Jancevska et al., 2012). The range of factors for children being born SGA include, but are not limited to, maternal and paternal influences and also genetic factors or disorders. Globally, 16% of infants are born SGA (Campisi et al., 2019) and 10% of these do not experience catch up growth and remain two SDs below the average height for their age and sex. Children with SGA who have gone for more than four years without experiencing catch-up growth are often considered for growth hormone treatment. The prevalence in a general paediatric population of children born SGA who qualify for GH treatment was 1:3250 so this is a widespread issue (Tamaro et al., 2021).

Being born SGA has been associated with problems in health-related quality of life (HRQoL), behaviour and cognitive development. Studies such as that by Goedegebuure et al. (2018) have shown that subjects who additionally received GH treatment have a significantly higher quality of life regarding positive emotions.

Norditropin SimpleXx is a drug used to treat growth failure in children due to a variety of causes including growth hormone deficiency, Turner syndrome, Noonan syndrome, reduced kidney function and SGA. In adults it can be used

to maintain the correct balancing of hormones. The active ingredient in Norditropin SimpleXx is the biosynthetic human growth hormone somatropin. Somatropin is classified as recombinant human growth hormone (rhGH). rhGH differs from pituitary-derived human GH (hGH) in that it is produced artificially, but has the same amino acid sequence.

rhGH is a relatively new innovation in the pharmaceutical field. In 1981, the first rhGH was developed and trialed using recombinant DNA technology. In 1985, a link between human pituitary GH and Creutzfeldt-Jakob disease (a fatal degenerative brain disorder) was discovered and use of human pituitary GH ceased. By the 1990s, hGH had been replaced by recombinant growth hormone. There are currently many brands of rhGH, including Nutropin, Humatrope, Genotropin and Norditropin – all produced by different pharmaceutical companies. However, all contain somatropin and are similar in efficacy, composition and cost, with the only differences being related to their formulations and delivery devices. This literature review will be mostly focused on Norditropin but will include articles related to all brands of somatropin as they are virtually indistinguishable from one another.

Although there have been many studies into the effects of rhGH and its cost effectiveness, most have grouped SGA without catch-up growth in with other causes of short stature. This literature review focuses on the use of rhGH in treating those born SGA who did not experience catch-up growth. It will evaluate both the length and cost of the treatment and the potential results and improvement in health-related quality of life due to the height gain provided by the treatment. The literature review will seek to compile articles related to the possible side-effects of the treatment and these will also be considered when evaluating the overall use of the treatment.

## **Methodology**

The literature review was conducted utilising three separate databases - PubMed, Google Scholar and MedRvix. To ensure the results were

relevant to the study, two key search terms were used, and these were 'SGA' and 'Norditropin'. (Referring to the brand of rhGH commercially known as Norditropin SimpleXx.) From these two search terms, 320 results were obtained from PubMed and 314 from Google Scholar. Using both search terms and 'Norditropin' on its own, no results were retrieved in MedRvix while using the search term 'SGA' alone returned 13 results. None of the MedRvix results were related to studies involving people born small for gestational age and treated with rhGH and so these could be discarded as irrelevant to the study.

In order to narrow down the 634 combined results from the PubMed and Google Scholar databases to those relevant to the topic, several exclusion criteria were applied. If any one of the following criteria were met, the article or paper was excluded from the literature review. Firstly, if the article was not solely focused on subjects receiving rhGH treatment due to short stature or GH deficiency caused by being born small for gestational age, the article was disregarded. This included articles where the focus was on other causes such as Noonan's syndrome and was done in order to prevent these other factors from influencing the results of the review. Next, the study was disregarded if it was not directly related to growth hormone treatment itself or if it was focused on growth hormone treatment for adults. This is because rhGH treatment is used for growth hormone replacement in adults, rather than growth failure as it is in children, and so does not treat the effects of growth hormone deficiency caused by being born SGA. Articles that were dated from before 2000 were disregarded as the use of rhGH has become more widespread since then. Articles focused on a geographical area outside Europe or North America were disregarded to enable more consistent height gain comparisons.

After the exclusion criteria were applied, 140 articles remained. Almost half of these were inaccessible, and many analyses were carried out on the same sources (notably the NordiNet outcomes study). Of those that could be used in

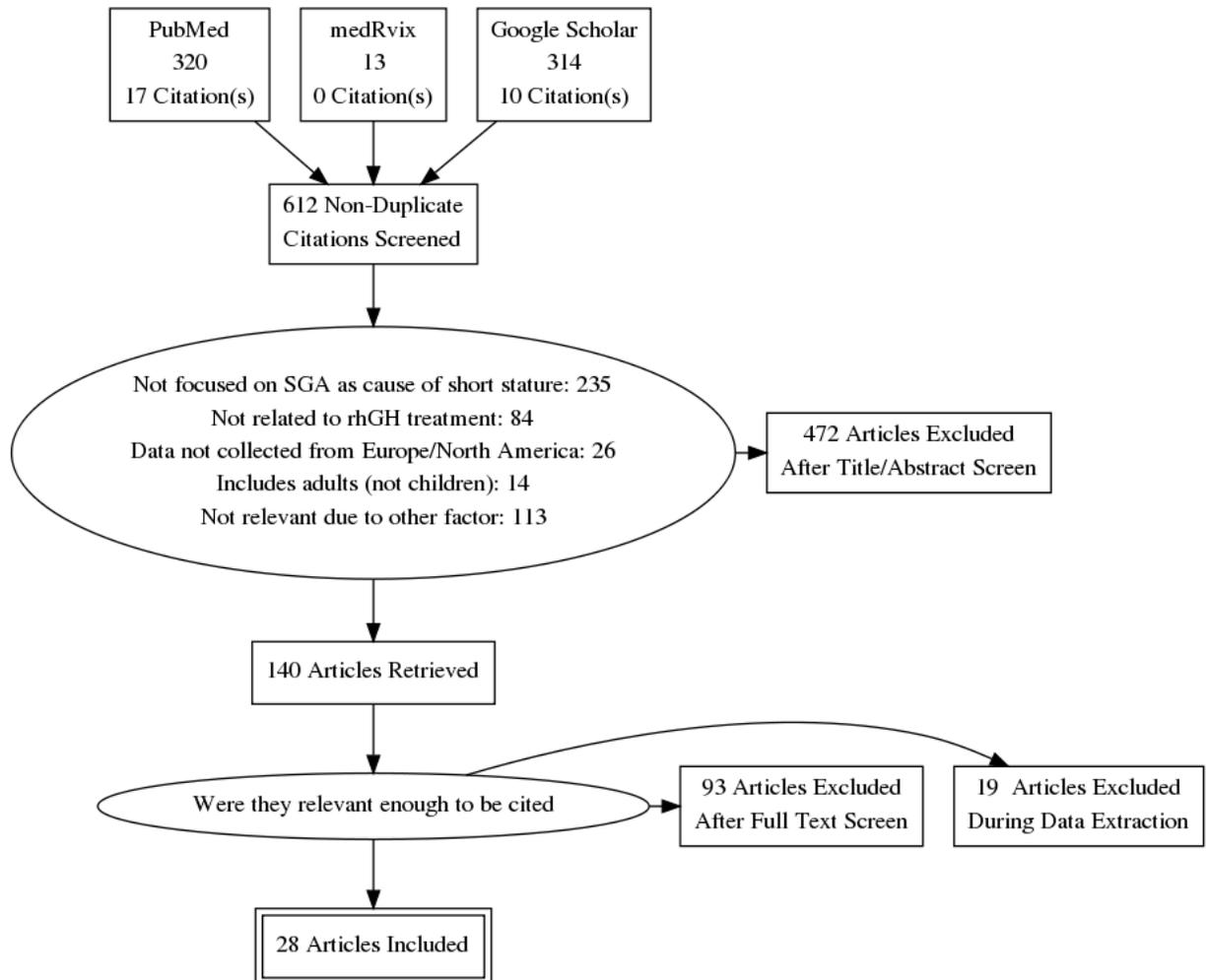


FIGURE 1: PRISMA flow diagram showing the process of the literature review.

the study, 28 were cited in the final literature review. The breakdown of this process is shown in figure 1.

## Results

### *Results in terms of height/growth velocity increase and influencing factors*

To evaluate the effectiveness of rhGH treatment, it is necessary to quantify the overall benefits of the treatment and weigh this against the costs and possible side effects. This is complicated by the fact that a 'good' height is subjective and the mean height of an average adult, accounting for sex, differs depending on the part of the world under review. In this review, I will consider the treatment successful based on how much it compensates for the catch-up growth that was

not experienced by 10% of children born SGA before treatment began, and thus how far it closes the gap between the initial height (<2SD below the mean) and the mean weight and height of the local population accounting for age and sex. It should be noted that although height change being expressed in SDS is generally considered more robust across age and gender than expressing change in cm, change in height SDS is not completely age-independent, because less variation is observed in height SD in younger vs. older ages as demonstrated by Lee et al. (2012). To make the comparison more equal, this will only include European and North American subjects where the average height is comparable - with 5ft 10.1 inches (1.78 meters) average for males in

Europe and 5ft 9.69 inches (1.77 meters) in North America. (NCD Risk Factor Collaboration, n.d.)

The analysis of two ongoing studies by Lee et al. (2012) including the NordiNet® International Outcomes Study (NordiNet® IOS) and ANSWER encompassed 4,582 subjects aged <18 who underwent GH treatment for two years. Out of these, 678 subjects were born SGA (and as they qualified for GH treatment, it can be assumed they had not experienced catch-up growth). In the total population, the mean change in height SDS after one year of treatment, for all indications, was +0.57 SDS. However, children born SGA responded better to the treatment with height SDS of +0.64, only slightly lower than the +0.67 increase in SDS experienced by patients with MPHD (another cause of short stature). However, after two years of treatment, children born SGA and treated had experienced the greatest gain of +1.03 SDS which was higher than the increase in other groups and the mean of +0.99 increase in SDS. In total, 45% of those born SGA reached a normal height within  $\pm 2$  SDS of normal height for age and gender. Although this percentage was higher for other groups in the study, the greatest height gain (and therefore likely the greatest benefit) was in children born SGA. The reason for the lower percentage reaching normal range despite the additional growth was due to children born SGA starting at a considerably lower baseline height in comparison to the other groups. It can therefore be inferred that GH therapy not only benefits children born SGA to a greater extent as they are more responsive to the treatment, but is also more needed for subjects in this category as they start with a lower baseline height. However, this lower baseline could be attributed to the labelling of SGA in Europe, as countries such as France required the child to be below -3SDS from the average height to qualify for medical reimbursement (Boguszewski et al., 2005).

Other studies provided further analysis of the full 10 years of the NordiNet® study. Although that study has not given final results, it shows the disparity in diagnosis in different countries

affecting growth outcomes, with lower dosages in Serbia and Montenegro and higher dosages in France. It also confirms that dosages decreased over time in all countries and that children born SGA were shorter than all other groups treated with GH therapy at baseline with a mean height SDS values well below -2.5 (Polak et al. 2018 ). Another study identified the mean final height of a group of patients at -1.2 SDS as corresponding to 172cm in males and 159cm in females (Dahlgren & Wikland, 2005).

The response to GH treatment can differ according to a number of factors including initial height velocity, dosage, age when treatment started and duration of treatment, sex and adherence (Nicolino et al., 2018). In a French study, out of 51 SGA patients, 31 were good responders. These good responders were not only taller at the beginning of treatment and had better starting growth velocities, but they were also younger when treatment began. This suggests the treatment has greater effects when started at a younger age as children treated for >2 prepubertal years experienced a lower height gain when undergoing puberty (Dahlgren et al., 2005).

Adherence also plays a key role in the effectiveness of the treatment. This was shown in a study of 110 Spanish patients, which concluded that adherence to the treatment was generally very high at 93.9% over two years of treatment in SGA patients - but was also important in determining the end result, as the frequency of patients with a height velocity > 1 SD from the norm was higher ( $p=0.025$ ) among patients with an adherence > 90% (de Arriba Munoz et al., 2020). It has been calculated that SGA children showed an increase of 0.6cm/year for each 10% adherence modification. Low adherence was observed in patients with lower pre-treatment height velocity and in patients whose parents had lower levels of education (Lee et al., 2019). In a survey of 116 subjects 75% of patients receiving rhGH treatment preferred the use of a new disposable pen, which is currently being introduced in the NHS in the UK, and if the new

FlexPro® pen delivery system fulfils its design to be easier to transport and use, it is possible adherence will increase among patients. When comparing two options of delivery devices, the NordiFlex (Norditropin) and GoQuick (Pfizer), it was concluded that the majority of patients preferred the NF to GQ and that the NF was more intuitive to use, as fewer mistakes were made using this mechanism (Kappelgaard et al., 2012). Finally, Sävendah et al. (2012) identified a significant difference between the genders in the 2-year response to GH treatment as well as in the prepubertal cohorts of SGA children. After correcting for dose, the mean baseline age and the initial height standard deviation scores, the change in height standard deviation scores was significantly greater in boys born SGA, suggesting a more varied response to treatment.

#### *Results in terms of cost effectiveness*

Over a patient's lifetime, somatropin (0.033 mg/kg/d) treatment was associated with a height gain of 16.12 cm and a cost per centimetre of height gained of £4,359. The incremental cost of somatropin treatment was £70,263, with a quality-adjusted life-years (QALY) gain of 2.95, resulting in an incremental cost per QALY of £23,807 - below the widely accepted cost-effectiveness threshold in the United Kingdom of £30,000 (Christensen et al., 2010). This study was focused only on children born SGA undergoing GH treatment, but it should be noted that it dates from 2010, so the cost per QALY may have decreased since.

When comparing adolescents born SGA without spontaneous catch-up growth, it was determined that the group treated with growth hormone scored significantly better in both health status and health-related quality of life in a disorder-specific questionnaire. This suggests that the boost in height provided by the treatment does translate into a better quality of life for the patient, which should be the true end goal (Bannink et al., 2005).

## **Other Effects of rhGH Treatment in Children Born SGA**

The effects discussed will be outlined below:

### *1. Association of GH treatment with cardiovascular complications.*

Two articles focused on the possibility of a link between childhood GH treatment and damage to the cardiovascular system. Tidblad et al. (2021) used a cohort study of 3408 patients treated with rhGH in childhood from 1985 to 2010 and followed up until November 31, 2014. It concluded that rhGH treatment was associated with increased risks of cardiovascular events in early adulthood (especially in women) but that conclusions of causality are limited, and overall risk remains low. Another study which assessed long term changes in blood pressure, lipid concentrations and carotid intima media thickness in order to assess cardiovascular risk factors in young adults born SGA after the cessation of GH treatment - but which only included 199 participants - came to the conclusion that long-term GH treatment in children born SGA has no unfavourable effects on cardiovascular health in early adulthood. The interpretation of the results even suggested that the treatment improved the lipid profiles of the patients (van der Steen et al., 2017).

### *2. Effect of the treatment on bone mineral density.*

One study, which included 88 subjects and so had a relatively small sample size, used dual-energy x-ray absorptiometry to measure bone mineral density (BMD) and this was compared with BMI and target height. This study recorded an improvement in BMD over the course of GH treatment, with almost all children in the study having an end result adult BMD within the normal range (Annemieke et al., 2013). This is consistent with the results of another study by Willemsen et al. (2007) in which a six-year follow-up of a randomised controlled GH trial also using DXA to investigate body composition and concluded that

the treatment resulted in an increase in bone mineral apparent density (BMAD).

### *3. Metabolic implications including effects on insulin sensitivity and risk of diabetes.*

In a study monitoring 26 children born SGA and treated with rhGH, it was concluded that there was no evidence to suggest future metabolic risk in young SGA children without catch-up growth, but that favourable changes in apolipoproteins were observed after one year of GH treatment in SGA children (Kojima-Ishii et al., 2018). A larger, randomised, double-blind trial with a population of 149 children born SGA from 8 different countries who received GH therapy delivered daily (using the NordiPen) found that GH only caused slight, non-significant improvements on total cholesterol and LDL cholesterol levels, although it maintains that longer GH treatment may be needed to explain the persistent benefits often reported in this regard. It also noted GH treatment reduced ghrelin levels through a negative feedback loop and so led to reduced fat mass, while glucose levels remained within the normal limits. It recorded a change in insulin levels, although this was reversible upon the discontinuation of the treatment, but further research is warranted to clarify the full effects (Lebl et al., 2011). It has been suggested that GH treatment results in higher fasting insulin and glucose stimulated insulin levels being observed and this is elevated with a higher dose of GH. Subjects born SGA also have an increased risk of developing diseases such as type 2 diabetes, hypertension, dyslipidemia and coronary heart disease and that the increased risk of type 2 diabetes may be a result of insulin resistance caused to SGA children having fewer  $\beta$ -cells. It is worth remembering that this lack of  $\beta$ -cells refers to all children born SGA (Delemarre et al., 2007).

### *4. Effects of GH treatment on Cognitive function and head circumference in children born SGA.*

Studies on this topic are limited. Being born SGA has been associated with lowered intelligence

and academic performance as well as behavioural problems. This randomised, double-blind trial of 79 children born SGA and treated with GH (with a mean duration of 8 years of treatment) showed a significant increase in Perforal IQ and Total IQ and this increase was positively related to head circumference (Hokken-Koelega et al., 2006).

### *5. Effects on fat and fat redistribution.*

After two years of GH treatment, children gained both weight and height and developed a less adipose body composition and these changes were accompanied by a more centripetal distribution of fat mass relative to those who did not receive treatment (De Schepper et al., 2007). Another study with a focus group of 35 short SGA children undergoing GH therapy (one group with a delayed start to treatment and another with a start not delayed for comparison) found that GH therapy contributed to not only a more normal body size and follistatinemia but also insulin resistance, hypo-HMW-adiponectinemia, hypertriacylglycerolemia and an amplification of the deficit in subcutaneous fat. The therapy moved height, weight and lean mass toward the norm. However, being born SGA is often associated with a high sensitivity to insulin and a low amount of subcutaneous fat, and the treatment led to an over-correction resulting in an insulin resilient state and an amplification in the deficit of subcutaneous fat (Ibáñez et al., 2010).

FIGURE 2: Table containing a summary of the effects of rhGH therapy in children born with SGA and a risk rating for each possible effect of the treatment.

Risk type	Effect	Additional notes	Risk Assessment
Cardiovascular risks	Increased risk of cardiovascular events	Often in women during early adulthood but no clear conclusions of causality	Low risk
	Changes in blood pressure	No unfavourable effects	No risk
	Changes in lipid concentrations	Treatment may improve lipid profiles	No risk
	Changes in carotid intima media thickness	No unfavourable effects	No risk
Effect on bone mineral density	Bone mineral density (BMD) / Bone mineral apparent density (BMAD)	Improvement in BMD / BMAD	No risk
Metabolic implications	Future/long term metabolic risk	No evidence to support future metabolic risk	No risk
	Changes in apolipoproteins	Favourable changes	No risk
	Changes to total cholesterol levels	Slight improvement	No risk
	Reduced fat mass	Reduces ghrelin levels through a negative feedback loop – leads to reduced fat mass	No risk
	Higher fasting insulin and glucose stimulated insulin levels while on treatment	Reversible on discontinuation - further research warranted	Medium risk – maybe linked to insulin sensitivity (see next point)
	Insulin resistance	May be an overcorrection of high sensitivity to insulin inherent in many children born SGA	High risk – could result in diabetes and heart problems
Effect on cognitive function	Increase in Performat IQ and Total IQ	May be linked to increased head circumference	No risk
Effect on fat / fat redistribution	Move toward the norm in weight and lean mass	Positive effect	No risk
	Amplification in the deficit of subcutaneous fat	Overcorrection to the lack of subcutaneous fat present in many children born SGA	Medium risk
	Development of a less adipose body composition	This is accompanied by a more centripetal distribution of fat mass relative to those born SGA and left untreated.	No risk
	Other abnormalities related to weight gain	Risk of developing hypo-HMW-adiponectinemia and hypertriacylglycerolemia	Medium risk

## Discussion and Conclusion

This literature review aimed to evaluate the effectiveness of rhGH therapy in counteracting the effects of being born SGA and not experiencing catch-up growth. Although 634 results across 3 databases were screened and 140 of these results matched the inclusion criteria, after further screening by abstract and removing inaccessible or outdated articles, only 28 were cited. The particular lack of articles in MedRxiv suggests that there have not been many recent additions to our understanding of the effects of GH treatment in children born SGA. This may change as the NordiNet® International Outcome Study and ANSWER programme® progress and more data is gathered on the overall effect of rhGH treatment, although the ANSWER programme is limited in the fact that the study is purely observational and may contain variations in data collection (Hoybye et al., 2013), (Rapaport et al., 2018).

Despite the lack of this long-term data, there is near unanimity that GH therapy provides an increase in growth velocity and moves the height of the subjects closer to the mean height for their age and sex. This change appeared to be particularly promising in those born SGA without catch up growth, and although fewer treated SGA children reached normal heights than those with other causes of short stature, this was due to them having a lower baseline height. The outcome of the treatment was affected by a wide range of factors, most notably the age that treatment started, gender and adherence. It also provided less benefit for those with the lowest starting height velocities and who likely would have benefitted most from more successful treatment.

Most of the effects not directly related to height are positive, as subjects have moved towards the norm in several areas including weight, lean mass, head circumference as well as Verbal IQ and Perforal IQ. BMD also increased. Although there was a slight increase in the risk of

cardiovascular complications in young adults treated with GH, this was minimal, and conclusions of causality are limited. The article claiming this (Tidblad et al., 2021) contradicted an earlier study by van der Steen et al. (2017) which claimed GH treatment has no metabolic downsides and in fact improves lipid profiles. Out of those discussed above, the most serious side effect is the over-correction of insulin sensitivity, resulting in insulin resistance and a higher likelihood of type 2 diabetes.

Overall, it appears the rhGH therapy is effective in improving the quality of life of children born SGA who did not experience catch-up growth and meets NHS guidelines on cost effectiveness. However, there is a lack of research on long term outcomes for the treatment, so this conclusion is limited to the first few years of treatment and further research is required.

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# Cognitive-behavioral therapy (CBT) for reducing implicit biases among healthcare professionals

Eugenia Calvo Prieto

Sha Tin College, Hong Kong S.A.R.

calvom1@stconline.edu.hk

## Abstract

An implicit bias, also known as an unconscious bias, refers to the unconsciously held thoughts, feelings, and behaviors towards a group of people or social identity. As an unconscious process, they are difficult to identify, manage, and control. In the healthcare system, they can increase health disparities by affecting patient-provider interactions through clinical decision-making, such as providing shortened consultation times or decreasing the probability of referral to specialists. Despite that, effective strategies have been discovered and implemented to mitigate the impacts of implicit biases; however, there is still a limited amount of research regarding the effects of these interventions on healthcare professionals. Additionally, the use of psychotherapy as a method to reduce implicit biases hasn't been extensively researched. A systematic review of literature was conducted to provide new insights into how cognitive-behavioral therapy (CBT) can alleviate the influence of unconscious prejudices and stereotypes in the healthcare profession. The two main mechanisms involved are identifying and promoting awareness of implicit biases, as well as reshaping irrational thinking patterns and fostering behavioral changes through techniques such as stereotype replacement, mental imaging, perspective taking, mindfulness, and individuation to mitigate unconscious biases. Further areas of research and interventions, including the creation of psychometric tests to identify unconscious stereotypes among physicians and assessments to measure changes in patient care and health, are also discussed.

*Keywords: cognitive behavioral therapy, implicit bias*

## Introduction

An implicit bias, also known as an unconscious bias, refers to thoughts, feelings, or behaviors towards a group of people or social identity that are unconsciously held or recognized. In the healthcare system, they can impact how healthcare professionals perceive, interact with, and treat patients (Capatosto et al., 2016), which can impact patient-provider interactions through treatment decisions and adherence, leading to inefficient healthcare delivery and poor health outcomes (Hall et al., 2015).

In the past, cognitive-behavioral therapy (CBT) has been proven effective in helping people find new ways to behave by changing negative or irrational thinking patterns (Davis & Saripalli, 2018). Although implicit biases can be reduced through effective strategies, there is a limited amount of research on the effects of these interventions among healthcare providers (Schnierle et al., 2019). Therefore, this systematic review aims to provide new insights into how CBT can promote awareness of implicit biases and provide strategies to mitigate the harmful impacts of these biases among physicians.

This review contains multiple levels of individuals, including a clinician who administers CBT, a physician who receives CBT to identify and tackle their implicit biases, and the patients visiting the clinic who may be impacted by the physician's implicit biases. While this article focuses mainly on physicians, CBT would most likely also provide a favorable approach to tackle implicit biases among other healthcare professionals, including

physician assistants, pharmacists, nurses, and experts in public or community health. To minimize confusion, the word 'clinician' will refer to the person administering CBT, 'client' and 'physician' will be used to refer to the physician receiving CBT, and 'patient' will be used when referring to the patient receiving care from the physician who is receiving CBT.

## Methods

With the COVID-19 pandemic being relatively recent, there has been an influx of literature surrounding the increased prevalence of health disparities due to various aspects of the pandemic for low-income persons and racial and ethnic minority populations (Kim et al., 2020). One of these aspects are the implicit biases held among healthcare professionals (Johnson-Agbakwu et al., 2020).

Based on a PubMed and Google Scholar search, to our knowledge, there have not been any studies focused on how CBT can be used to reduce implicit biases among healthcare professionals, both during the pandemic and amidst other health situations. A systematic literature review was performed, allowing for reproducible methods to identify, select, and assess all relevant research related to this topic. This analysis was conducted by surveying articles in PubMed and Google Scholar with the predetermined set of search terms, such as "implicit bias," "cognitive behavioral therapy" and "CBT." Other search terms to broaden sensitivity while maintaining specificity included "implicit racial bias," "implicit prejudices," "implicit bias healthcare," "implicit bias among physicians," "how to reduce implicit bias," and "reducing implicit bias among healthcare professionals," which yielded (n = 44) relevant papers to be screened.

From the papers screened, (n = 11) articles were excluded due to publish date (older than 15 years), credibility (not peer-reviewed), language (other than English), and relevance (focused on other psychological processes that cause bias and affect health disparities; not focused on

implicit stereotypes and prejudices against groups of people but rather animals, inanimate objects, etc.).

This allowed for (n = 33) full-text articles to be assessed for eligibility, which were evaluated thoroughly on whether they should be considered for the final qualitative synthesis. In the end, (n = 8) full-text articles were excluded.

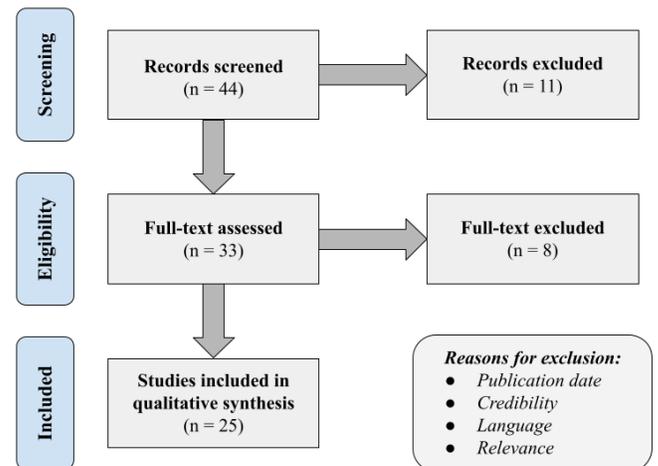


FIGURE 1. PRISMA Flow Diagram showing the vetting process of this systematic review of 43 articles.

Some of these articles only explored the importance of reducing implicit biases, rather than the techniques and strategies that could be used to mitigate the impacts of these stereotypes. However, research about implicit biases and their mitigation strategies in contexts other than medicine, such as education or the general population, was also included to provide a robust analysis of the literature on the topic, given the limited amount specific to the association between implicit bias and CBT. This would also avoid the possibility of overlooking evidence that could still be relevant to the research question, allowing for the adaptation of current implementation strategies for healthcare workers. Ultimately, 25 articles were included in the final qualitative synthesis.

Additionally, websites from national agencies, trusted organizations, and medical textbooks,

such as Mayo Clinic and the National Health Service (NHS), were used to supplement details and provide basic insights about the methods of CBT. Content was compared across multiple sources to ensure this research study was reliable and credible.

A weakness of this research method is the exclusion of many relevant papers that were not written in English. Since implicit biases are a natural and universal phenomenon that everyone possesses, this could have offered novel and valuable perspectives into how CBT could be applied to reduce implicit bias among different groups of people and social identities.

## **Implicit Biases**

### *What is an implicit bias?*

An implicit bias, also known as an unconscious bias, refers to thoughts, feelings, or behaviors towards a person or group of people that are present but unconsciously held or recognized, affecting our actions and decisions without us realizing. They are an example of the brain's fast, automatic, intuitive, and unconscious (implicit) thinking mode as one is not aware of them, making them difficult to acknowledge and control (Hall et al., 2015).

### *How do implicit biases impact the healthcare system?*

Implicit biases can impact how healthcare professionals perceive, interact with and treat patients (FitzGerald & Hurst, 2017), especially among physicians who provide care to disadvantaged populations, including racial/ethnic minorities, the poor, sexual minorities, the mentally ill, the overweight or obese, and the disabled (Capatosto et al., 2016). This can be shown in patient-provider interactions through clinical decision making (e.g., doing more or less diagnostic work, chronic disease management), causing poor health outcomes, leading to higher disease prevalence, lower life expectancy, and increased mortality among these social groups of people (Hall et al., 2015).

Therefore, it is important to assess strategies to reduce these biases among providers.

### *Examples of implicit bias among healthcare professionals*

A common form of implicit bias is an implicit racial bias, which is when individuals prefer people of a particular race unconsciously. Many healthcare providers often have an implicit bias in terms of positive attitudes towards White people and negative attitudes towards people of color (Hall et al., 2015), which has led to several racial health disparities in the US and has hurt patients from marginalized racial populations.

Another common form is an unconscious gender bias, which are automatic mental associations formed on how we judge people based on traditional feminine and masculine assigned traits, stemming from traditions, norms, values, culture, or experience (The Bureau for Employers' Activities & International Labour Organization, 2017). These biases can greatly contribute to health disparities by gender (Chapman et al., 2013).

Other common forms of implicit bias is lesbian, gay, bisexual, transgender, and questioning (LGBTQ+) bias. In the healthcare system, LGBTQ+ individuals are known to experience higher levels of health disparities compared to the general population, resulting in a lower standard of care or restricted access to healthcare services among these patients (Sabin et al., 2015). These biases can also cause patients to delay seeking care due to past experiences with discrimination (Simpson et al., 2013).

### *Causes of implicit bias*

One common cause of implicit bias is that we, as humans, like taking mental shortcuts. In general, our brain uses knowledge about past regularities, patterns, and associations to generate predictions about what is expected to occur, compared to what has actually happened. This is thought to be an evolutionary development that ensured survival among the human family's

earliest ancestors to quickly decide whether a person, animal, or situation encountered was likely to be friendly or dangerous. Long later, one's brain can still use these tendencies to categorize everything experienced (Marcelin et al., 2019). However, this could unwittingly get in the way of healthcare professionals attempting to establish genuine and empathetic relations with their patients (Hall et al., 2015) if practitioners become reliant on their unconscious stereotypes and inaccurate cognitive shortcuts to guide clinical decisions (Rynders, 2019).

Another reason is social and cultural influences. Although most people would reject negative ideas associated with disadvantaged groups (Glas & Faloye, 2020), these marginalized groups are often portrayed in disparaging settings when one is growing up, which could impact decision-making later on in life (FitzGerald & Hurst, 2017).

Consequently, research has shown that children use group membership unconsciously to guide attitudes and stereotypes towards groups of people. These groupings are rooted in early development—children begin to recognize what distinguishes them from others and believe that what is similar to them is 'good' and what is different from them is 'bad' (Baron et al., 2014). Forming negative opinions and associations about outgroup members early on in life can contribute to the development and aggravation of implicit biases.

### **How can cognitive-behavioral therapy reduce implicit biases among healthcare professionals?**

#### *What is cognitive-behavioral therapy (CBT)?*

Cognitive-behavioral therapy (CBT) is a form of psychotherapy that focuses on how thoughts, emotions, and actions are all interconnected and can negatively impact each other in a vicious cycle (National Health Service, 2019).

CBT's main purpose is to identify inaccurate, overwhelming, or negative thinking patterns; view challenging situations more clearly; and break these down into smaller parts. It has

been proven as a very useful tool to treat mental health disorders and help people manage stressful life conditions. Traditional CBT treatments are usually spread over 5 to 20 weekly or fortnightly sessions, with each session lasting from 30 to 60 minutes (Mayo Clinic, 2019).

#### *Identifying troubling situations or conditions*

The first step of CBT is to identify troubling situations, conditions, or problems that are disrupting the life of the client (Mayo Clinic, 2019). In the context of applying CBT to reduce implicit biases among healthcare professionals, this step would include identifying cognitive biases.

To do this, physicians could take one or more Implicit Association Tests (IAT) (Edgoose et al., 2019). This test operates by categorizing words and images into one of two categories (e.g., Fat/Thin; Good/Bad) and measuring the strength of associations between these concepts and evaluations (i.e., social groups and identities), as either slight, moderate, or strong (Project Implicit, 2011).

Psychological research has also shown that unconscious biases can cause subtle changes in the behavior of healthcare professionals when treating patients. This can include smiling less, verbally dominating conversations, and providing less eye contact (Capers, 2020). Since healthcare professionals (and all other individuals) are unaware of their unconscious biases, they would not realize the stereotypes that guide their patient interactions. Therefore, they could be expected to deny these biases if questioned.

Despite that, oftentimes, clients may be brought into CBT by peers, such as partners or employers, that have pressured them to go against their own will (Sokol & Fox, 2019), thus CBT can potentially be used as a treatment to recognize implicit biases not only for healthcare professionals who believe that there might be something wrong but also for those who reject this. From here, the problem can be identified, and the other steps of treatment can be planned and implemented.

### *Identifying negative thoughts, emotions, and behaviours towards the problem*

The second step of CBT is to identify negative or irrational thoughts, emotions, and behaviors towards the problem (Mayo Clinic, 2019). In this context, this step would include promoting awareness of the physicians' own unconscious biases and understanding their impact on patient care. This can be done in various ways. This might include learning and educating providers about what implicit biases are and their impacts on clinical decision-making. Another important part of this approach would be educating oneself about different groups of people and cultures as well as learning what language and behaviors could come across as offensive or hostile. A recent systematic review investigated methods to reduce LGBTQ+-related implicit biases among healthcare professionals (Morris et al., 2019). It was deduced that programs designed to increase provider knowledge of the LGBTQ+ community (e.g., understanding sexual orientation and gender identity) through lectures and interviews, could prove successful in reducing implicit biases. Similar programs could be implemented to increase knowledge representing a variety of aspects related to patient health from stigmatized groups to help providers recognize and create new values and attitudes towards these groups of people.

### *Reshaping and challenging negative, inaccurate, or irrational thinking patterns*

The final step of CBT is to reshape and challenge negative, inaccurate, or irrational thinking (Mayo Clinic, 2019). In this case, this step would include fostering a behavioral change to reduce the influence of these biases among providers.

CBT is based on the cognitive model. This is a model that shows that perceptions of an initial situation are what actually influences and triggers reactions, feelings, and physiological responses towards the conditions, not the situation itself

(Sokol & Fox, 2019). Situations in which actions taken by healthcare professionals are impacted by implicit biases can lead to health disparities. However, it would also mean that the provider has responsibility for their response after becoming aware of their own biases in the previous stage of treatment and would mean that their behaviors and attitudes are changeable and can become more rational. This could be done by implementing strategies that allow practitioners to manage their implicit biases.

One strategy could be stereotype replacement, which involves recognizing that a response is stereotypical, reflecting on why this happened, and considering how a biased response could be replaced in the future (Brown et al., 2021). For example, if a physician was treating a patient from a minority population, they might directly jump to conclusions and base their opinions on their predictions about the patient's different treatment adherence capabilities. They would directly assume that the patient would not comply with the medication, therefore, the physician might not provide the appropriate medication and consequently treat the patient disparagingly. However, if the physician replaces this stereotype and asks the patient if they can comply with this medication, this will open discussion about alternative treatment options (if necessary). It would also allow the provider to engage in positive interactions and increase contact with stereotyped group members, which can reduce implicit biases by changing and improving cognitive associations and representations of the group.

Additionally, research has strongly supported the use of mental imaging to replace automatic responses involving stereotyping of others. These people could be abstract (e.g., modern Native Americans), famous (e.g. Barack Obama or Lin-Manuel Miranda), or non-famous/personal (e.g. a close friend or a teacher). This strategy works by making positive examples more salient in the mind and making them easily accessible if placed in a situation that could show implicit biases (Edgoose et al., 2019).

Another retrospective approach could include perspective-taking, which involves taking the first-person perspective of an individual in a stereotyped group, increasing psychological proximity towards the group, and improving automatic or impulsive irrational group evaluations (Devine et al., 2012). Studies have shown how perspective-taking can increase patient satisfaction and can be used as a useful technique in clinical practice and decision making (Blatt et al., 2010). Overall, this technique would help physicians build empathy and teach them to pause, think, and reassess situations in which they have interacted with individuals from a stereotyped group or when societal stereotyping has been observed, allowing re-evaluation of how a patient may feel about certain treatment options or diagnostic tests. This would allow providers to operate more effectively in relation to fulfilling their role in eliciting therapeutic change (Moudatsou et al., 2020). It would also encourage practitioners to be active bystanders in situations where unintentional prejudiced actions occur among peers. An example of this could include watching videos and listening to presentations of patients from affected groups who describe their experience with discrimination in healthcare settings, which can have a powerful and long-lasting impact and increase cultural humility (Sukhera et al., 2020).

Another alternative approach could be mindfulness, to improve coping abilities and biological reactions that influence attention, emotional regulation, and habit formation. Since cognitive shortcuts are often used under pressure or in response to complex time-limited decision-making conditions (Bogetz et al., 2021), this technique could be especially helpful for physicians who often experience these circumstances due to their stressful work environment (Wong, 2008). Current research has already established that mindfulness could reduce discriminatory behaviors and cause people to rely less on their instincts (Lueke & Gibson, 2016). Therefore, mindfulness could be used to mitigate implicit biases by increasing

physicians' awareness of their ability to control potentially biased responses and reducing sources of cognitive loads, such as stress or burnout. This could be done through meditation, yoga, or connecting with nature.

Another potential approach is individuation, which involves acquiring specific information about affected populations to allow providers to associate patients with unique attributes rather than group-based and possibly discriminatory attributes (Devine et al., 2012). This helps prevent inaccurate, stereotypic, or prejudicial assumptions towards individuals and is rather simple to apply since a physician's individual identity is likely to intersect with their patients' social groupings, such as sexual orientation, race, ethnicity, or gender.

Additionally, after treatment has started and strategies have been learned, physicians must still remember to deliberately reflect on their unintentional biased actions to help open discussion about interactions with patients from stigmatized groups, which is important in reducing stereotype activation and application (Marcelin et al., 2019).

#### *Strengths of using CBT to reduce implicit bias*

One strength of using CBT to reduce implicit biases among healthcare professionals is that it incorporates a continuous process of improvement, practice, and reflection (National Health Service, 2018). This would be necessary to ensure that these unconscious biases are mitigated, instead of using single educational approaches or awareness campaigns. It teaches the physician methodical and practical strategies that could be used in everyday clinical contexts, even after their treatment has finished.

Additionally, CBT can be provided in many different formats, including groups, self-help books, and apps. This can be especially advantageous in combating implicit biases among several people in healthcare institutions.

Another important thing to remember is that even if cognitive-behavioral therapy isn't used to directly mitigate implicit biases and rather to

reduce the negative effects of stressful situations, it can still reduce the effects of these unconscious biases. Clients often try cognitive behavioral therapy to stop negative thinking patterns that make individuals feel anxious or scared (National Health Service, 2019). Implicit biases are more common in stressful or time-limited conditions and, since doctors are particularly prone to this, CBT could provide a framework for physicians by helping them be more optimistic and less negative towards these pressuring situations.

#### *Weaknesses of using CBT to reduce implicit bias*

One weakness of using CBT to reduce implicit biases is that CBT focuses on the person's capacity to change their thoughts, feelings, and behaviors.

Therefore, this approach would not address or consider any wider problems in systems or families that could have an impact on the physician's implicit biases (National Health Service, 2018), such as the influences and beliefs of peers that have caused the provider's implicit bias and are further exacerbated by often being surrounded by these people. This could impact attitudes and reduce the effectiveness of the therapy.

Furthermore, the focus of CBT is focused on the present and specific issues and is problem-oriented (Fenn & Byrne, 2013). This would mean that it does not address the underlying causes of unconscious biases among healthcare professionals, such as a narrow-minded upbringing, etc.

#### **Conclusion**

In summary, the mechanisms of cognitive-behavioral therapy (CBT) can be used to mitigate implicit biases among healthcare professionals by 1) identifying the implicit biases, 2) promoting awareness of the unconscious biases and recognizing their impact on patient care and health, and 3) teaching and implementing strategies that help reduce implicit biases. Mitigating the impacts of unconscious biases is essential since they can still be held even if the

physician claims to have egalitarian beliefs and aims to provide quality healthcare for all individuals.

Research has revealed a need for more information investigating the impacts of these implicit biases on patient health and care and how they can be reduced among physicians (Maina et al., 2018); therefore, this systematic review aimed to provide a methodical way to do this, by both raising awareness of physician subconscious biases and providing potential cognitive and behavioral interventions of the management and reduction of implicit biases among physicians to reduce healthcare disparities. This form of psychotherapy also aims to provide continued exposure in reducing these biases to fully integrate the information into other knowledge and skills, since real changes in the healthcare professionals' implicit biases have not been shown with one-time training or educational approaches in the past.

Despite this, there were several limitations to this systematic review. Firstly, there was a limited amount of literature on the effective implementations that could be used to reduce implicit biases, so there was not a substantial amount of information on the question of this research paper. In the future, more research needs to be conducted on each of the mentioned specific cognitive and behavioral interventions to extensively examine and assess their effectiveness for healthcare professionals, as well as improvements that could be made or new strategies that could be implemented.

Another limitation is that this research topic mainly focuses on the interpersonal causes of implicit biases. Therefore, it does not consider situational factors in healthcare that could exacerbate these unconscious stereotypes. One of these factors is the lack of diversity in healthcare. This presents additional barriers to addressing health inequity and creates work environments that are at risk for defensiveness, passivity, and apathy in healthcare. There has already been evidence that increasing diversity in the healthcare workforce could improve

healthcare delivery, especially to underserved groups of people in the general population (American College of Physicians: Internal Medicine, 2010). CBT can also be applied to the wider clinical population (e.g., as group therapy) to further evaluate and mitigate systemic prejudices and stereotypes that drive inequalities in healthcare institutions. Another factor is the medical curriculum and its impact on physicians' ways of processing information. Medical education prioritizes pattern recognition, which relies on combinations of signs and symptoms to suggest diseases that are helpful in the clinical context. However, it can increase the possibility of healthcare professionals directly using these potentially stereotypic thought patterns when experiencing stress, pressure, or unfamiliar situations, promoting inaccurate and inconsistent clinical decision-making and judgment (Brown et al., 2021). This might include directly thinking that a White child with recurrent respiratory infections would have cystic fibrosis—even though these diagnoses are based on true prevalence rates, they may not always apply to individual patients (Marcelin et al., 2019). Another major factor is a physicians' busy work schedule. Attending regular CBT sessions can take up a large portion of time (National Health Service, 2018), which would be especially inconvenient for most physicians that work between 40 to 60 hours a week and a quarter of physicians who often work 61-80 hours a week (American Medical Association, 2015). Therefore, using CBT to reduce implicit biases might not be feasible for physicians in some cases.

Despite these weaknesses, this research paper can provide new approaches to combating the issue of implicit biases among physicians. There are various recommendations for what can be done in the healthcare community to minimize implicit biases. For instance, to identify the various types of implicit biases, more non-standardized measures also need to be designed by researchers to assess the amount of knowledge that physicians possess about the discrimination faced by stigmatized patient groups in the

healthcare system. This would allow knowledge gaps to be pinpointed that may be causing implicit bias and provide background information for how CBT could be used to reduce these biases among physicians. Assessments to complement the Implicit Association Test (IAT) that focus specifically on diseases and environmental and physical influences on health (e.g., lifestyles) that are stereotypical among certain groups of people, could be used to do this. For example, if a diagram representing sickle cell disease came up, and there were three options: a Black person on the left of the screen and a White person on the right, physicians might be more likely to choose the left option due to their unconscious stereotypes about the association between diseases and social groups/identities. Researchers have also highlighted the challenge of measuring changes in implicit biases, so this is also an important issue to be investigated in future studies. Moreover, examining reduction strategies for specific patient groups (e.g., Black individuals, gay and lesbian people) lends further insight into the types of strategies that are most effective for reducing the implicit bias of those individuals among physicians.

Furthermore, physicians should also continually renew their training in the medical field to lessen the effects of these cognitive biases. This could be done through continuing medical education (CME), which aims to help healthcare professionals maintain their competence and learn more about new and developing areas in the field of healthcare (National Institutes of Health (NIH), 2017). In this case, CBT could be applied in this area of continuing education to discuss how implicit biases can impact health disparities and help physicians develop strategies to mitigate unconscious stereotypes in daily interactions with patients. However, there could still be potential weaknesses to this. For example, certain countries and healthcare institutions have different requirements of what can and cannot be included as part of a physician's CME credits, so this idea may not be feasible in some situations. As well as that, the healthcare professional would

generally choose certain CME credits depending on their own interests, therefore, it would be unlikely for a practitioner to purposefully pick a CME credit on implicit bias if they aren't aware of these biases. A potential solution to this is to assess the practice management of the healthcare provider before choosing a CME credit. For example, this could be applied through an inspection (e.g. surveys, interviews, etc.) of patients treated by the physician to see if they believe that they have been receiving the best quality of care from the practitioner. If they haven't, then physicians should be encouraged to choose a CME credit to mitigate the impacts of their implicit prejudices in clinical judgment and decision-making.

Overall, to fully achieve health equity, medical practitioners and institutions have a responsibility to cultivate awareness and mitigate the damaging impacts of unconscious biases on patient management and health, to provide a high quality of care to all patients.

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# Islamic Feminism's relation to the Western Feminist movement and Sharia Law

Aryan Chaudhary

Ryan International School, Noida, India  
aryan.chaudhary010505@gmail.com

## Abstract

The ever-growing Feminist movement seeks to dismantle the status quo of the existing unjust patriarchal system. To further understand the effect and extent of the feminist movement, it is essential that we move away from the Western Feminist movement and see how the movement has transformed into different shades, also covering the issue of religious derived Islamic Law (Sharia Law), as discussed in this paper. The current structure of Sharia Law and the fatwas (formal rulings/interpretations given by Islamic Scholars in response to questions from Islamic courts) given in legal systems that follow Sharia Law has been seen to clearly in support of the existing patriarchal system the feminist movement seeks to dismantle (Asokan, 2019). Hence, this paper explores how women part of the Islamic Feminist Movement are changing Islamic Law and how the Islamic Feminist movement compares with the Western Feminist Movement. A comprehensive review of literary material has been done on the Qazi court system and kinship laws in India, Sharia Law's relation and advancement in the feminist movement. In addition, literary works that seek to relate the Western Feminist movement and the Islamic Feminist Movement have been read and analysed.

*Keywords: Feminism, Islam, Sharia Law*

## Introduction

Islam is a religion that began around 1400 years ago with the Prophet Muhammad, and currently is the second most followed religion around the world with around 1.2 Billion (Table: Religious Composition by Country, in Percentages, 2012) people identifying themselves as Muslim. With Western (the word Western in the paper is used to include countries from both Europe and the Americas, with the primary focus covered in North America, in the form of discussions of multiculturalism in Canada etc.) portrayals of the feminist movement being largely secular, we often struggle to see the middle ground between religious values and the secular feminist perspective. It cannot be denied that the western media often seems to portray Islam as a religion dominated by patriarchy (Sugianto et al., 2021). Muslim males are often portrayed as inherent predators (Wigger, 2019), and we can see how this generalisation can lead to not only social misconceptions, but also institutional structural stratification unjust for Muslims, for example, after the unification of Germany. After the unification of West and East Germany, many German politicians like Vera Lengsfeld, who despite being in the Liberal Party after the unification, has been quoted to have said,

“The newspapers and television stations say that I have a pathological fear of Islam. The truth is that I really am afraid of Islam. But why is that pathological and not reasonable? Most Muslims are peaceful, it's said. That is true. And yet, every time I pass a woman wearing a headscarf, I ask myself, what are you trying to tell me? That you're

different than me? That you're better than me? That my granddaughters are going to be walking around like that one day.”

Furthermore, this narrative is evident in the development of the 'Leitkultur' debate in Germany and the interpretation of the 'Alternative for Germany' party (Lewicki, 2019). Many Islamic Feminists' like Aabiya Baqai, argue that Islam is already feminist and that the way Islamic leaders have interpreted the Holy Quran and Hadiths is in such a way that they can easily assert their patriarchal norms, and that the feminist lens of the Holy Islamic texts show a picture that is polar opposite to what we think it of as today (TEDx Talks, 2017). The method that Islamic Feminism takes is where the patriarchal interpretations of the Holy Islamic texts are challenged and thus, this method is where the religious values and the objectives of the western feminists come together. Below is presented an in depth analysis of the differences and middle ground between Western and Islamic Feminism, and ways how female Muslim scholars are challenging interpretations of the Sharia Law, and a very creative example of how women are stepping up in India and taking control of Personal Islamic Law against the unjust concept of Triple Talaq (also known as Talaq-e-Biddat), and giving judgements that hold adjudicatory power in the Indian plural legal system to not only female kinship disputes, but also providing counselling for the cases where there is even a slight hope of reconciliation between Muslim couples (Dutta, 2021). I argue that by further exploration of the link in Islamic Feminism and its interpretation of the Holy Texts, that a healthy link relation between religious beliefs and the feminist movement can be established, and in turn, challenging the various radical violent Islamists groups and their claim of 'following the word of Allah', which they use as a justification for violence.

## **Contextualising Islamic Feminism in Relation to Western Feminism**

### *Defining Islamic Feminism*

To really grasp the complexity and different opinions in this area of study, it is essential to analyse what the extreme sides in both Islamic Communities and in the Feminist movement think. To start off, let us further analyse how Western Media defines Islam. You can often see people in Western Media refer to the radical branch of Islam as 'Fundamentalist'. The first search on Google on the meaning of Fundamentalism gives us a result where Fundamentalism is defined as 'relating to or advocating the strict, literal interpretation of scripture', and we can see how calling radical Islamists fundamental is false, as the interpretation of Islamic scripture is highly subjective in nature as mentioned above, and this association calls Islam as inherently something that supports radical ideas like Jihad and flawed interpretations, which is very wrong, as we will see throughout this paper (Irawan & Arifin, 2021). On the other side of the spectrum, we see how current patriarchal communities in Islamic societies see the Feminist movement as a threat and thus naturally seeks to impose ideas that are in opposition of the Feminist movement, as seen in Post-Revolutionary Iran, for example. (Asokan, 2019) Now that we have explored the polar opposites of this crossroad of intersectionality, we can see how when both sides merge, there is bound to be conflict in people's minds, however, if we were to really define the scope of Islamic Feminism as a movement, it would be accurate to note that it is an extension of the feminist movement against patriarchal structures, which takes ideals from Islamic religious texts, namely the Quran and the Hadith, with their own interpretation of scriptures.

### *Contrasts with Western Feminism*

Islamic Feminism, which has roughly been defined in the previous paragraph shows the basic difference of the movement even within majority Muslim populations. The dimensions of Feminism in Muslim population are something that is key to

note as there is a very big distinction between 'Secular Muslim Feminism' and 'Islamic Feminism' where Islamic Feminism finds the Holy texts to be the primary source of their feminist value, where the Secular Muslim Feminist movement, as the name suggests, doesn't rely on religious affiliations for their values. The Secular Muslim Feminist takes many perspectives from the Western Feminist movement while keeping their experiences as a Muslim in mind, and thus the distinction between the two subgroups is important (Akalay, 2021). The Secular depiction of wearing a hijab, for example, takes on a different discussion between the Islamic Feminists and not just Western Feminists, but Western depictions in general, with one side debating it to be a part of their culture and the latter debating and showcasing it as a part of oppression (Kasiye, 2021). This is one of the issues that causes the Islamic Feminists to move away from Western Secular Feminism, as the hijab they argue is very important to Islamic culture and in actuality enhances their beauty (Shikha et al., 2020). However, this is not to confuse that the end goal of both shades of the Feminist movement are same, i.e., equality, but the methods of both groups achieving their goals is the where the difference lies.

#### *Irshad Manji's Canadian Islamic Feminism*

Irshad Manji's case study of trying to balance the Western and Islamic ideas of feminism is a very controversial yet interesting example. After viewing many interviews and book excerpts from Irshad Manji's works, it is best that we start by understanding her situational context, i.e., multiculturalism in Canada, as Irshad herself describes Canadian Multiculturalism in an interview as essential to her migration from Uganda to Canada (The Agenda with Steve Paikin, 2014). One of the landmark laws in multiculturalism in Canada can be seen in the form of the Canadian Multiculturalism Act (1988) established two fundamental principles, which were that – a) all citizens have the freedom to preserve, enhance and share their cultural

heritage; b) multiculturalism in Canada promotes the full participation of individuals and communities in all aspects of Canadian society (Canadian Ministry of Justice, 1985). This Act was in direct correlation with Former Canadian Prime Minister Pierre Trudeau's declaration of Canadian Multiculturalism long before in 1971 (Banting, 2010). We can see how the differentiation between 'full participation of individuals' as mentioned earlier and cultural participation of groups are essential. This distinction between individual views and the views of the groups can be related to the idea of 'group honour' that is prevalent not only Islam, but can also be seen in Indian Hindu communities to what we refer nowadays as 'honour killings', for example, the 2009 Shafia Family Murders in Canada (Jiwani, 2017), which showed in its fullest, the flaws of groupthink of cultural participation in Canadian Multiculturalism. However, it is of use to note over here that culture and real Islamic Holy Texts are very different from each other, as culture is a result of the development of the Islamic Holy Texts, and these developments have already discussed to have been supporting patriarchal norms, and thus, a different interpretation of the Holy Texts can gradually change culture as well. Irshad Manji goes on to say that Canada in its specificity to being really good at multiculturalism (Brosseau & Dewing, 2018), has unfortunately created a space where people are so afraid of being called racists, and thus, they go on not opposing even the customs that are evil and require changing. Irshad Manji adds on by saying how there needs to be a safe space to discuss and support critical thinking in contrast to what is actually occurring currently, i.e., just being nice to one another (The Agenda with Steve Paikin, 2014).

#### **Shariah Law and Islamic Feminism**

While the meaning of the word 'Shariah' has evolved overtime, In the 7th century, during the lifetime of the Prophet Muhammed, the word roughly translated to 'the way'. This meaning can lead to the clear definition of what Sharia really is.

Sharia is not a set of fixed rules, but rather a series of moral and ethical principles derived from the Quran. Sharia Law on the other hand, is an interpretation of these moral and ethical principles which has been turned into a legal code. Thus, it is essential that we understand that Sharia Law in itself is based on interpretation and can be changed. As this paper is being written, the importance of this relation with Sharia Law and Islamic Feminism is of more importance than ever, with the Taliban recently capturing Kabul in Afghanistan and declaring their intention to rule according to their interpretation (“What Is Sharia Law? What Does It Mean for Women in Afghanistan?” 2021). It provides a different way of attacking radical Islamist ideals, by attacking their interpretation of the Holy Texts itself, a method that will question the very ideals of such extremist groups.

#### *Feminist interpretation of Sharia Law*

Among the differences in the Feminist movement in Muslim countries, as discussed above in the form of Secular Muslim Feminism and the Islamic Feminist movement, we can see how the approaches of these subgroups are very different when it comes to dealing with the Patriarchal interpretations of Islam and countering them to achieve women’s rights. The Secular Muslim Feminist movement often questions the very legitimacy of Sharia in the legal systems in countries, whereas the Islamic Feminist Movement challenges those patriarchal interpretations of the Quran, and provide their own perspective to the issue (Dalaman, 2021). One example can be seen in the huge difference in interpretation in the Quran about the controversial legality about male figures “justified” use of abuse on their spouses. The argumentation of radical Islamists lies in the 34th verse of Surah An-Nisa which states –

“Men are the caretakers of women, as men have been provisioned by Allah over women and tasked with supporting them financially. And righteous women are devoutly obedient and, when alone, protective of what Allah has

entrusted them with. And if you sense ill-conduct from your women, advise them ‘first’, ‘if they persist, ’ do not share their beds, ‘but if they still persist, ’ then discipline them ‘gently’. But if they change their ways, do not be unjust to them. Surely Allah is Most High, All-Great.” (Surah An-Nisa - 1-176, n.d.).

We can clearly see how the verse is very subjective in its interpretation like many other verses in the Quran. First, the word ‘gently’ creates subjectivity as to the magnitude of punishment, and at the same time, the verse doesn’t define a type of punishment. Despite these gaps, radical Islamists seek to justify domestic violence and other horrific acts, which in actuality, holds less to no basis in interpretation of this specific verse. This is only one of the verses that hold a lot of subjectivity in Islam, and this is what Islamic Feminists seek to use to dismantle patriarchy and achieve equality, which is the ultimate goal of even feminism, while at the same time, Islamic Feminists achieve a balance between their religion and identity, while fighting the evils of the Patriarchal system. It is not difficult to see how the theological base of Violent Islamist groups like Al Qaeda can be challenged, and once the Islamic Feminist approach gains traction and relevance in the Muslim communities, there will be no base for such groups to grow on.

#### **Qazi All Female Muslim Court System**

Perhaps the most standout of all the proofs of the rapid evolution of Islam’s interpretation to be more female-centric comes from the establishment of the ‘Bhartiya Mahila Muslim Andolan’ (Literal translation- Indian Muslim Women Revolution) in 2007.

An autonomous, secular-rights organisation based in Mumbai, India that works for the citizenship rights for Muslim women, with the hope of tackling secular issues in the form of their inclusion outside personal Muslim Law as well. The organisation began training women Qazis in 2012 (BMMA, n.d.). The Qazi is a name given to a judge in the Sharia Law who plays several key roles, including legitimising marriages.

While the organisation's work, when put into a broader timeframe, seems strange (women have historically been prohibited from being Qazis), it is actually well founded in Islam's very roots. According to Ebrahim Mossa, Professor of Islamic Studies at the University of Notre Dame, "There are no teachings in either the Quran or the prophetic tradition that prohibits women from being Qazis. Even the wife of the Prophet Muhammad, known as Sayyida Aisha, performed and solemnised the nikah of several people." (The Rise of Female Sharia Judges in India, 2019). To also combat against the traditional material taught to 'Qazis-in-training' that has traditionally been centric of the masculine world view, the BMMA has developed its own syllabi for female Qazis (Bhatt, 2017). BMMA's sociological study, extensively written about in 2015 and 2016, revealed that over 95% of poor Muslim women hadn't even heard of the All India Muslim Personal Law Board (Niaz & Soman, 2015), an independent organisation that is responsible for the continuity and implementation of Muslim Personal Law in India (All India Muslim Personal Law Board, n.d.). This puts the need for female Qazis in the limelight- if women are not even aware of the decision makers, how can they be assured that their woes would be heard and their needs adequately represented at the highest levels? While the BMMA still continues to be criticised by some Islamic leaders who deem women being Qazis is against Sharia Law, the positive response for the female judges has been incredible- with over 150 cases for the 15 judges and numerous multicultural weddings being legitimised by them (Mohta, 2019). It is important to note that while the female Qazi is not recognised by the state, it runs on its legitimacy in the neighbourhood, taking the example of Khatun Shaikh, a female Qazi judge who created a network with local police, lawyers and civil servants to create a legitimate backing from the neighbourhood. This system of connections gives authority to the Qazi judges and makes their judgements carry heavy weight in those societies

despite not being recognised by the state (Dutta, 2021).

## Conclusion

This literary review establishes the relationship between three main issues, these are, the Islamic Feminist Movement, the Western Feminist Movement and Sharia Law, while further providing examples and arguments to explore the polar opposites and relations between these parts that can be related to each other. The western portrayal of Islam, and the subsequent analysis of how Islamic verses' when viewed from a feminist perspective shows a very different story from what the Islamic customs and structure of Sharia Law that exists in the contemporary world. Further exploration has revealed how Irshad Manji, a Canadian educator on issues like Islam and Feminism, analyses the relationship between multiculturalism in Canada and the reality of what extreme Canadian multiculturalism can translate into, and how this issue can be tackled. The paper also explored the feminist perspective on the Quran in the form of verse 34 of Surah An-Nisa in the Quran. The Qazi courts in India shows us the Islamic Feminist movement in action, an interesting example of Feminist Islamic Law in action. The implications of this research is to facilitate a discussion to form a bridge between religious values and the Feminist issues, as mentioned before, and using the Feminist interpretation to challenge the radical Islamist consensus that leads to many forms of Gender-based discrimination.

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# Can Two People Process Different Things Based on Differences in Cultural Identity?

Emily Nam Cho

Asia Pacific International School, South Korea

emilycho6125@gmail.com

## Abstract

Can cultural differences influence how people perceive and subsequently recall visual stimuli? East Asians tend to holistically process visual stimuli by attending to relationship, whereas Westerners tend to analytically process by attending to focal features. Previous aging studies suggest that older adults relative to younger adults bind target and distractor items despite attempts to inhibit distractors, which benefits subsequent explicit learning. Through implicit exposure to word-picture pairs in a 1-back task, we investigated whether there were cultural differences between East Asians and Westerners on an explicit learning task using similar stimuli. East Asians are likely to process visual stimuli holistically (e.g., Lao et al., 2013), so we predicted that they would bind the target picture and distractor word together, facilitating explicit learning. Conversely, we predicted Westerners to analytically process words and pictures separately, with successful inhibition of the distractor word, resulting in no facilitation on the explicit learning task. We found differences that suggest East Asians are engaging in binding. This may suggest that bottom-up perceptual processes occur concurrently to top-down attentional inhibition, interacting to influence memory recall dependent on cultural identity.

Keywords: culture, visual processing, attention, inhibition

## Cultural Differences in Visual Processing

Given the same picture, could two people see different things based on differences in cultural identity? Jenkins and colleagues (2010) investigated cultural differences in visual processing in a functional magnetic resonance imaging study that involved presenting participants with objects against congruent or incongruent backgrounds. They found that East Asians showed greater neural activity when focal objects mismatched the background context when compared to Westerners, suggesting that East Asians holistically processed these visual stimuli by focusing on the relation between foreground objects and background context. Conversely, Westerners engaged in analytic processing by independently processing focal features and background context. Furthermore, Chua and colleagues (2005) tracked eye movements when East Asian and Westerner participants viewed scenes. They found that East Asians more often looked at the background whereas Westerners spent more time looking at focal features. This indicates that there are cultural differences in overt attention paid to visual stimuli. Taken together, these studies show that East Asians and Westerners do exhibit differences in visual processing of scenes, owing to differences in where overt attention is directed.

These cultural differences in visual processing between East Asians and Westerners apply to object processing as well. Kitayama and

colleagues (2003) first presented participants with a diagram of a rod that was surrounded by a frame and had participants either reproduce the exact length of the rod or an equivalent proportion of the rod given differently sized frames. Westerner participants were more accurate at reproducing the exact length of the rod independent of the frame given to them, supporting the view that they analytically process each feature independent others. Conversely, East Asians were more accurate at reproducing lengths of rods in proportion to the provided frame size, suggesting that they initially holistically processed the rod in relation to the surrounding frame. Supporting this cultural difference in object perception, Lao and colleagues (2013) found cultural differences in a task that asked participants to classify Navon figures, basic shapes that are constructed from smaller shapes. Westerners were quicker to classify analytically similar figures (e.g., a square made of circles and a triangle made of circles are similar based on the features that make up the whole). Conversely, East Asians showed repetition suppression in an attentional component of electroencephalogram measurements (i.e., P1) for holistically similar figures (e.g., a circle made of squares and a circle made of triangles are similar based on the bigger picture formed from the smaller shapes). That is, East Asians showed more neural efficiency when processing objects holistically rather than analytically. These two studies show that there are cultural differences between East Asians and Westerners in object perception based in attention, similar to scene perception.

A previous study investigating attentional inhibition on subsequent explicit learning found differences in performance by age, rather than culture (Campbell et al, 2010). Older and younger adults were asked attend to specific features of visual stimuli (i.e., pictures) and inhibit distracting features (i.e., superimposed words). Older adults were found to less successfully inhibit the distractor and instead bind words and pictures together, which benefitted them in a later explicit

learning task. Given that East Asians holistically process visual stimuli based on the attention they give to relationships between features, we wondered if they would exhibit similar binding patterns between word and picture that could subsequently benefit them in an explicit learning task. We investigate this idea by implicitly exposing both East Asian and Westerner younger adults with word-picture visual stimuli during an attentional inhibition task and subsequently testing recall on an explicit learning task. Given that East Asians holistically process visual items, we expect binding to occur between word and picture in the initial implicit exposure, resulting in better explicit learning of word-picture pairs that were previously exposed. Conversely, we predict that Westerners will analytically process target pictures independently of distractor words, resulting in no benefit in a subsequent explicit learning task.

## **Methods**

### *Participants*

Participants were a convenience sample of 22 younger adults (ages 18 to 25 years,  $M = 18.64$ ,  $SD = 1.64$ ; 9 males, 13 females). They were undergraduate students at the University of Illinois Springfield Seoul Campus and received partial course credit for their participation. A total of 25 participants were recruited, though data from three participants were not analyzed because they did not follow instructions, their cultural identity did not match that of the experimenter, or they were not tested at their chronotype peak. Of these remaining 22 participants, 11 were East Asian participants and 11 were Western participants. East Asians were recruited to be of 'East Asian descent, i.e., Korean, Chinese etc.', whereas Westerners were recruited to be of 'European descent, Caucasian'. All participants were required to be native English speakers because English words appear as stimuli within this study.

### *Procedure*

East Asian and Western participants were matched with an experimenter of the same cultural identity to make cultural identity more salient. After we obtained informed consent, participants proceeded with a 1-back task, some filler tasks, an explicit learning task, and a working memory task. In the 1-back computer task, participants saw stimuli constructed from a black English word superimposed over a red line drawing (see Figure 1) presented sequentially on a computer screen. Participants were instructed to attend to the picture as the target and ignore the superimposed word, responding by pressing the spacebar whenever the target picture occurred twice in a row. Following this, participants completed two visuospatial filler tasks, the flanker task and the hidden patterns task, for a total of ten minutes. In the flanker task, participants responded to left or right arrow symbols (e.g., '>' or '<') that appeared at the center of a letter string by one of two buttons representing left and right. The hidden patterns task was a paper task, where participants searched within a series of line figures and indicated whether a model line structure can be traced within them. Participants responded with an 'x' in the presence of the model line structure, and 'o' in absence. Next, participants completed an explicit learning task using similar word-picture stimuli used in the initial 1-back task, without reference to this first task. They first studied sixteen of each word-picture pair for two seconds each, and subsequently verbally recalled the English word when given the picture as a cue. There were two conditions for these word-picture pairs. Eight 'maintained' pairs were the exact word-picture combination that participants saw in the 1-back task, and Eight 'disrupted' pairs were constructed from previously seen picture and words but in a novel combination. The study test procedure was repeated three times. To ensure that participants were not aware that the stimuli in the explicit learning task were previously implicitly shown in the 1-back task, we questioned participants for any similarities they found

between tasks. At the end of the study, participants were given the operation span task. In the operation task, participants were instructed to read the equation aloud, verify its accuracy by saying "yes" or "no," and then read the target word aloud. Immediately after finishing reading the target word, the experimenter advanced the program to the next equation/word pair. Once all of the equation/word pairs for a trial had been shown, they were asked to recall all of the target words from that trial by saying them aloud in the same order in which they were presented. Scores were calculated by summing the number of words correctly recalled in any order. Finally, we interviewed each participant for demographic information on cultural background. Participants were also given a package of questionnaires to complete at the very end of the experiment.



Figure 1. Prototypical word-picture pair that was shown to participants to illustrate the idea of superimposition before a practice trial.

### *Measures*

Participants filled out several questionnaires after the experiment, including the Morningness-Eveningness Questionnaire (MEQ; Horne and Östberg, 1976), Shipley Institute of Living-2 Vocabulary Subscale (Shipley, 1940), and the Asian Suinn-Lew Questionnaire (Suinn et al., 1987). Younger adults peak in performance during the afternoons (e.g., Goldstein et al., 2007), so the MEQ was administered to verify that participants were not morning-type, because the experiment was only run in the afternoon (between noon and 5pm). The Shipley-2 is a measure of English fluency and was used to exclude any participants with scores under 20,

because English words were used as stimuli. Finally, only East Asian participants filled out the Asian Suinn-Lew questionnaire, which measured the level of acculturation to Western culture. This measure was not administered to Westerners because many questions could not be answered if the participant was not of East Asian descent.

### Design

This study had a 2 (culture) x 3 (trial) x 2 (pair-type) mixed design. Cultural identity is a between-subjects variable, whereas trial and pair-type are both within-subjects variables. Performance on the explicit learning task was analyzed across the three different study-test trials and two word-picture pair-types (preserved, disrupted).

### Results

Accuracy on the 1-back task was calculated as the percentage of hits minus false alarms. Overall, Westerners (M = 92%, SD = 13 %) and East Asians (M = 91%, SD = 13%) did not differ in detecting repetitions,  $t(50) = 0.28$ ,  $p > .7$ ,  $d = .028$ .

Number of words recalled was submitted to a mixed analysis of variance (ANOVA) with culture as a between-subjects factor and Pair type as a within-subjects factor. The significance level for all statistical tests was  $p < .05$ . The improvement in trial showed that by the second and third trial, participants were performing at ceiling, recalling a mean of more than 7.5 out of eight pairs correctly. Given this, we focused on exploring data within the first trial. There was a reliable main effect of pair type,  $F(1, 51) = 5.64$ ,  $p = .021$ ,  $\eta^2 = .101$ , and culture,  $F(1, 51) = 5.36$ ,  $p = .025$ ,  $\eta^2 = .097$ . The two-way interaction of culture and pair type was not significant,  $F(1,51) = .130$ ,  $p = .720$ ,  $\eta^2 = .003$ . To further examine the effect of cultural group, we ran separate analyses for each cultural group. Overall, East Asians recalled more preserved pairs than did Westerners,  $t(26) = 2.49$ ,  $p = .01$ ,  $d = 7.33$  (see Figure 2). However, memory recall of disrupted pairs did not differ

between Westerners and East Asians,  $t(26) = 1.44$ ,  $p = .16$ ,  $d = 4.97$ .

Performance on the operation span task was also analyzed. Number of words correctly recalled did not differ between Westerners (M = 71%, SD = 9.9%) and East Asians (M = 75%, SD = 12%),  $t(26) = 4.76$ ,  $p = 6.30$ ,  $d = 13.63$ , demonstrating that they do not have fundamentally different working memory limits.

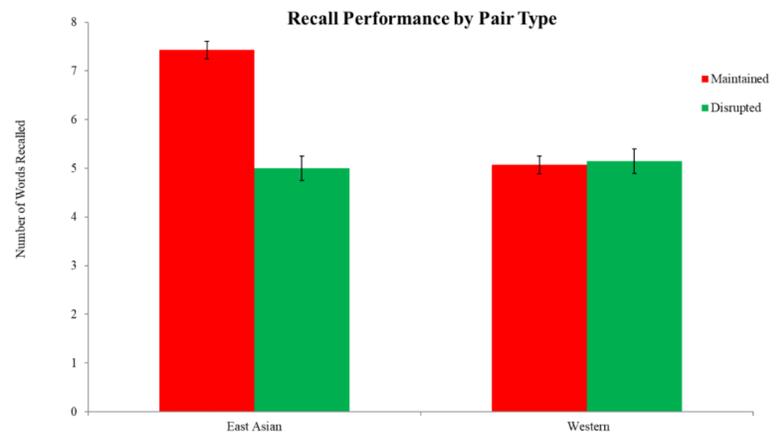


FIGURE 2. Mean number of words correctly recalled in trial 1 of paired-associates task. Error bars represent one standard error of the mean. In the experiment, there were eight preserved and eight disrupted picture-word pairs.

### Discussions

To recap, through implicit exposure to word-picture pairs in a 1-back task, we investigated whether there were cultural differences between East Asians and Westerners on an explicit learning task using similar stimuli. East Asians are likely to process visual stimuli holistically (e.g., Lao et al., 2013), so we expected that they would bind the target picture and distractor word together, facilitating explicit learning. Conversely, we expected Westerners to analytically process words and pictures separately, with successful inhibition of the distractor word, resulting in no facilitation on the explicit learning task.

Both of our repeated measures ANOVAs, across all data or just trial one showed significant effects

of practice across trials and differences in learning across pair-types. More importantly, significant cultural differences were found between East Asians and Westerners. Post-hoc analyses revealed differences between cultures in their pattern of recall across pair-types. Whereas Westerners performed similarly regardless of pair-type, East Asians were impaired on recalling disrupted pairs when compared with maintained pairs. This suggests that East Asians do engage in some binding between words and pictures in the initial 1-back task. This in turn facilitates their explicit learning when these pairs remain intact in maintained pairs or impairs explicit learning when these pairs are reshuffled. This could be suggestion that East Asians bind pictures and words due to holistic processing. East Asians may be attending to the relation between the word and picture rather than the independent features themselves, consistent with previous scene and object perception studies (Jenkins et al., 2010; Lao et al., 2013).

Adaptations to the current design may address some of the concerns that have been raised. Given that younger adults are performing similarly regardless of culture, but also at ceiling by second and third trials of the explicit learning task, increasing the difficulty of the task may help further parse apart any culture difference in younger adults. This can be done by reducing the length of time that younger adults view the word-picture pairs at study phase of the explicit learning task or increasing the total number of word-picture pairs to greater tax memory load. To investigate whether the differences in culture may be due to initial perceptual binding, we can adapt the explicit learning task to no longer require the segregation of features. Instead, we could have a recognition task where participants recall have to match the entirety of the word-picture pair, thus matching the hypothesized holistic processing at both prior exposure and explicit learning recall phase. Finally, we had recruited East Asian participants on the basis of being native English speakers, a control measure that was included

because English words were used as stimuli. East Asian, who are native English speakers, would have likely grown up under the influence of Western culture. This is reflected in the Asian Suinn-Lew Questionnaire scores, with East Asian participants scoring on average 3.02 out of five, indicating that our East Asian participants more likely identified as bicultural rather than purely East Asian. To emphasize the difference in cultures, we could alternatively recruit international students fluent in reading in their native language and adapt our stimuli to match the language of these participants.

Overall, we found subtle differences between East Asians and Westerners in attentional inhibition and subsequent explicit learning, possibly accounted for by differences in initial perceptual binding. This may suggest that bottom-up perceptual processes occur concurrently to top-down attentional inhibition, interacting to influence memory recall dependent on cultural identity.

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# Effect of strength training on bone growth and development in children and adolescents

Edward Cho

Belmont High School, United States  
echo22@belmontschools.net

## Abstract

Strength training is very common in adults and it has become more and more popular in children and adolescents. Strength training is designed to improve physical strength and endurance and it's often associated with the use of weights. There has been a concern that strength training could potentially stunt youth's growth by damaging their growth plate and putting too much stress on the growing body. This systematic review is to summarize previous and current studies on the effects, both positive and negative, of strength training on growth in children and adolescents. The effects of strength training were defined as its impact on bone growth, which is affected by growth hormone and sex hormones, including testosterone and estrogen. In this review the correlation between strength training in adolescents and potential risks/benefits to their height was explored. While there are both risks and benefits associated with strength training, the results suggest that properly designed and supervised strength training increases bone strength and decreases sports-related injuries and bone fracture risks, by increasing growth hormones, testosterone and bone density. Therefore, strength training has more benefits than harms to growth. In conclusion, strength training in a safe and well-supervised environment can positively improve body development as well as the height growth of adolescents with no negative effect on youth body growth.

*Keywords: height growth, strength training, children, adolescents, bone density*

## Introduction

Strength training exercises are not only for adult trainers but also have become increasingly popular in youth and adolescents for sports training, fitness programs, and physical activities (Stricker et al., 2020). Specifically in competitive sports, strength training is a popular practice to gain competitive advantage since it builds muscular strength and promote muscle formation. Even those who do not participate in sports have found interest in using forms of strength training to procure muscularity (American Academy of Pediatrics Council on Sports Medicine and Fitness et al., 2008). Due to the recent popularity in strength training among youth athletes and adolescents, it has been a controversial topic whether strength training can be beneficial or harmful to height growth of children.

Height growth is an important part of youth development. It is generally accepted that height is mostly determined by genetics, but environmental factors play important roles as well. Studies in twins have shown that approximately 80% of height is heritability, leaving the remaining 20% to be dependent on environmental factors like nutrition and exercise (McEvoy et al., 2009). In children and adolescents, bones grow in length because growth plates in the bones are not closed. At the end of puberty, growth plates fuse and bone growth slow down and stop growing. Normal bone growth is controlled by a number of hormones, including growth hormone, thyroid hormone and sex hormones. Growth hormone is

the most important factor and sex hormones, testosterone or estrogen, are important for pubertal growth.

Strength training including weightlifting has been perceived by some researchers to have negative effects on the growing body, especially height growth of a child. Therefore, some researchers have reached the concord that strength training is harmful to adolescents and would stunt height growth. Therefore, the ongoing myth has pushed back many of those who wanted to gain muscle strength to achieve their desired muscle mass whether it is for their self-esteem, or to stimulate athletic development (Granacher et al., 2016). Studies on negative effect of strength training show that potential injuries induced by improper use of weights can stunt growth. Growth plates are highly susceptible to injury in children because they are the last segment of the bone to solidify and tend to be weak. Fractures to growth plates (that are not treated properly) may cause the bone to grow abnormally since growth plates are crucial in determining length of the mature bone; the ramification could be a crooked arm or even a leg that is shorter than the other (AAOS, 2014). Otherwise, no direct investigation to prove that strength training will hinder the heights of pubescents has been performed.

On the contrary, other studies have shown positive impact of strength training on growth development. The majority of the fitness community has reached a consensus that, as long as the child is using the weights properly and taking the right precautions, strength training will not limit a child's height but might even increase it; medical and fitness expertise now encourage children to train strength as it strengthens bone density, tendons, and ligaments while also drastically reducing risk of future injuries (Imbo, 2015). Although it may be proved that height will not be hindered, the possible increases in height is still in question. There is a correlation between strength training and higher production of growth hormones, testosterone, and bone mineral density, which are all crucial in regulating the

growing body and even impelling height growth (Richmond & Rogol, 2016).

By systematic review of conflicting reports on the correlation of strength training and bone growth and development, his study shows that, under proper supervision, strength training can successfully improve body growth and development of children and adolescents by collectively increasing bone density, growth hormones, and testosterone and by strengthening skeletal muscles.

## Methodology

A systematic literature review methodology was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009), enabling for various differing perspectives surrounding the common myth to be taken into account and analyzed. This study was conducted by using a specific set of search terms (i.e., "strength training" AND "adolescents") that were inputted into academic databases PubMed and Google Scholar (few academically reputable websites, which included information from databases and professionals, were also tracked by the same search terms). Any article that included the growth of a youth was included in order to broaden understanding of research while still sustaining the relevancy of the question. Additional research based on references was also performed to find relevant search terms (such as "growth hormones") that may have an indirect impact to height.

Out of the yielded results from the search, relevant papers (n=71) were screened. Papers excluded from the research are the ones that did not discuss the specified age range (children and adolescents ages 8-20) of the subjects in topic, talked about a specific group of people not targeted in the investigation (ex. strength training impact on people of obesity or cerebral palsy), or was irrelevant (focus on a different aspect of the effects of strength training other than growth). Articles (n = 27) were traced on a document where they were thoroughly evaluated for their

quality, application, and creditability. A PRISMA 2020 checklist was implemented to help guide the process and document reference information (Page et al., 2021).

Of the full text articles that were evaluated, articles (n=6) were excluded because they discussed more towards growth of pubescents in maturation/ weight or discussed of the psychological stress-related injuries to the distal radius in female height growth. Other articles that were not directly focused on the correlation of strength training and height but included factors of height that may be insightful (ex. Study of growth hormones, testosterone, and bone density), were included in the study. Authors that had differing viewpoints were both used as it brings diversifying information of the potential benefits and risks of strength training. Figure 1 depicts the method of research in further simplicity.

## Results

This systematic review has provided four different aspects to be considered: risks of injuries in strength training, bone density, growth hormones, and testosterone. Skeletal injuries to the bone are incredibly prone to have a negative impact on height as well as the bone density, which is why they were included. Growth hormone and testosterone were considered as major hormones known to have anabolic effect on bone growth during puberty. Testosterone possesses strong androgenic and anabolic effects that are important for both women and men, although men produce significantly more testosterone than women.

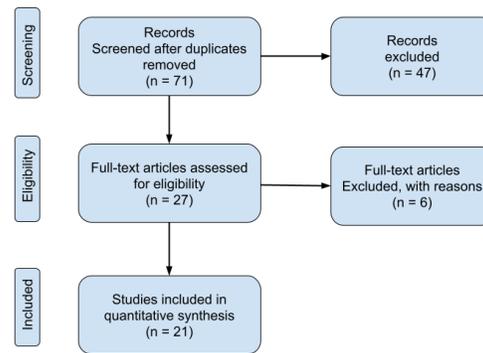


FIGURE 1: PRISMA flow diagram.

### *Risks of Injuries in Strength Training*

The common myth that the use of strength training by adolescents and children will be detrimental to their height originated from the misconception that injuries are frequent potential injuries to growth plates that may be deleterious to linear growth. Starting from the 1970s and 1980s, resistance training (a type of strength training mainly to increase the size and strength of skeletal muscles) was not advocated for youth due to the postulated “high risk” imminent when performed; data from the National Electronic Injury Surveillance System (NEISS), stated the increasing trends of growth plate injuries within youth lifers (Bubnis, 2018; Faigenbaum et al., 2011). While the NEISS did not specify the cause of injury that is most prevalent from strength training, data suggests that 40% to 70% of all strength-training injuries derived from muscle strains, most commonly in the hand, low back, and upper trunk (American Academy of Pediatrics Council on Sports Medicine and Fitness et al., 2008).

However, studies have shown that most injuries resulting from strength training are due to improper usage of weights or the absence of professional supervision of the child. One incidence of a 16-year-old football player indicates that he attempted to bench press 48 kg of weight without any assistance, resulting in a fracture of the left distal radius with dorsal displacement (Faigenbaum et al., 2011). Improper usage of weights is only subject to cause injuries. Injuries to back and trunk are commonly demonstrated because of adolescents'

impulse to build “mirror muscles”. This focus on building muscle mass brings about the principle of improper training because the child is using weights that is neglecting other important muscles like the core and trunk when training, leading to the persistent soft tissue injuries (Myers et al., 2017). According to surveyed study on UK students ages 13-16, practice of Olympic weight lifting and weight training reported an injury rate of 0.0012 per 100 participation hours (Barbieri & Zaccagni, 2013). Similarly, strength training experimental programs were studied and out of 10 studies, 3 reported injuries; injury rates of 0.176, 0.053, and 0.055 per 100 participant-hours, respectively (Myers et al., 2017).

Strength training isn't the only exercise that holds a probability of injury to the growth plate. While growth plate injuries are usually caused by a sudden event, they can also occur gradually; repeated stress inflicted on the bone through participation in competitive or recreational sports can intensify the likelihood of injury (AAOS, 2014).

It is reported that approximately 15 to 30 % of childhood fractures are injuries to the growth plate (Bubnis, 2018). Lastly, a study done on Canadian and Belgian boys have shown that there is no difference in stature and growth rate between those who participated in trainings and those who did not participate in trainings (Malina, 1994).

### *Bone density*

Strength training has been shown to have a positive impact on the bone, including bone mineral density; strength training in youth is able to strengthen bone mineralization and be beneficial to bone density (American Academy of Pediatrics Council on Sports Medicine and Fitness et al., 2008). Similarly, GH and IGF-1 are found to have essential interventions in bone growth through the promotion of chondrocyte proliferation and differentiation. GH and IGF-1 appear to act interdependently, in which together they regulate the bone growth and remodeling, to influence longitudinal growth and bone strength. The cartilage growth plates are made up of three

layers: the resting zone, proliferative zone and hypertrophic zone. Within the resting zone, GH performs to induce chondrocytes that differentiate and proliferate, and in both the proliferative and hypertrophic zones, IGF-1 induces differentiation and an increase in height within the columns of cells. (Blum et al., 2018). Additionally, physical exercises induce improvements in bone density, mass, and size. A study done on prepubertal boys required 10 jumping intervention 3 times per week for 7 months and results displayed a significant improvement in bone mineral at several bone regions (Richmond & Rogol, 2016). Similarly, to the adolescent wrestler mentioned above, deficit energy intake through excessive or over training may be detrimental to the bone. Still ample levels physical activity has shown to enhance optimal bone strength and is therefore recommended for children and adolescents.

### *Growth hormones*

The fundamental endocrine system that regulates linear growth in children is known as the growth hormone (GH)–insulin-like growth factor (IGF)-1 axis, which is made up of hormones, growth factors, and amino acids; the GH being a strong regulator of the IGF-1 secretion. GH-IGF-1 axis function disorders can severely influence growth potential. While GH is the predominant hormone responsible for somatic growth, most of the effects of GH are moderated through IGF-1, including long bone growth. For example, secretion of IGF-1 in cartilage cells of the growth plates have shown to have direct effect. (Blum et al., 2018; Roemmich et al., 2001). Growth hormone deficiency patients have lower concentrations of IGF-1, approximately 70% compared with age matched norms, linking short stature to the level of IGF-1 in children (Ranke et al., 2004). Furthermore, physical activity in children has shown to be critical to tissue growth and anabolism and has also demonstrated the increase of GH and IGF-1, as well as rapid growth. Exercise has shown to induce an increase of IGF-1; IGF-1 is believed to perform a big role in

building muscle mass through strength training. Pubertal status has shown to be a determinant in GH response to acute exercise where the children more advanced in his or her pubertal stage is shown to respond with a greater GH concentration (Richmond & Rogol, 2016).

With the heightened participation in competitive sports and physical activity, concerns regarding the aftermath of excessive training potentially stunting growth, due to the negative impact on the GH-IGF axis, have risen. In a study on in prepubescent female gymnasts, following 3 days of intensive training (3.5-5.5 hours daily), the concentrations of IGF-1 had decreased by 25% while there was no change in GH levels. (Richmond & Rogol, 2016). Moreover, it has been stated that participation in competitive sports that do not use weights have not appeared to have delayed puberty or change in growth. Conversely, there have been very few cases of slow of growth and maturation among some sports that have weights integrated in their training. Sports like gymnastics and wrestling have demonstrated this risk by the experience of energy depletion to the extent that there is a combination of extreme energy expenditure and restricted energy intake; greater output of energy than intake. On average, adolescent wrestlers expends about 800 kcals per practice, practicing about 2.5 hours a day for 5-6 days a week. With this in mind, it has been found that wrestlers actually intake 50% less than recommended. This under-nutrition taken by youth wrestlers may cause disruptions in the GH-IGF-1 axis, vital in determining rate of growth and pubertal maturation (Roemmich et al., 2001).

### *Testosterone*

Injections in testosterone have proved to improve first year height velocity of young children with constitutional delay of growth and puberty, without affecting the final height (Giri et al., 2017). Although testosterone has not been proved to increase (or decrease) the height of adolescents, it enhances muscle hypertrophy, strength, endurance, and power. In a study of male junior elite weight lifters ages 16 to 18, following a

normal session of intensive weight lifting, there was a 32% increase in testosterone concentration. Another study in male triathletes with an average age of 15, displayed significantly higher concentrations of testosterone after 16 training sessions in a 2-week period. Young athletes after a session of strength training resulted in a lower increase in testosterone concentration (Richmond & Rogol, 2016). One study tested the hormonal response to high power resistance exercise by taking the serum samples of testosterone (as well as cortisol and lactate) before and after lifting sessions of "10 × 5 speed squats at 70% of system mass (1 RM + BW) with 2 min inter-set rest intervals". Results showed a very large effect size for testosterone; high power resistance exercise produces acute increases in testosterone (Fry & Lohnes., 2010). However, there have been no studies that have linked the higher production of testosterone and growth height but is something to consider in further studies as it may prove to have an indirect positive effect.

### **Discussion**

These results indicate the fallacy of the negative relation associated between strength training and growth of children and adolescents, indicating that this training may not stunt height growth. Numerous studies have shown that strength training holds minimal risk and under the proper conditions (adult supervision, proper amount of weight and techniques taught by professional trainer, etc.), it would be safe and may not disturb the growth of height in adolescents and pubescent kids (Dahab & McCambridge, 2009; Malina, 2006; Bubnis, 2018; Malina, 1994; Roemmich et al., 2001). Health benefits that are yet to be found to have direct influence to height (testosterone and bone density) demonstrate the positive impact strength training has on the entire body, not limited to just height growth.

TABLE 1: Summary of benefits, plausible risks, and ways to reduce risks of strength training.

Benefits	Plausible Risks	Ways to reduce risks
<ul style="list-style-type: none"> <li>No found negative impact to height</li> <li>Low risk of injury (proper form)</li> <li>Higher production of GH/ IGF-1</li> <li>Improvement in bone density</li> <li>Increases in muscle strength, mass, and growth</li> <li>Boosts in self esteem</li> </ul>	<ul style="list-style-type: none"> <li>injury to growth plates</li> <li>Muscle strains</li> <li>Soft tissue injuries</li> <li>energy expenditure and restricted energy intake: potential slow of growth</li> </ul>	<ul style="list-style-type: none"> <li>Use proper form and weights</li> <li>Seek guided training from professional</li> <li>Increase nutritional intake</li> <li>Build all core muscles; do not focus just on “mirror muscles”</li> </ul>

Some limitations of this systematic review involve the lack of literature revolving around the direct consequences that strength training holds on the height of the growing body, although much data was found about risk of injuries, GH, and IGF-1. More research targeted towards the stress that weight lifting puts on the bones or growing body should be investigated since gradual skeletal risks were not included very much in this study. Further studies may include the application of strength training on those with skeletal or growth diseases such as osteoporosis and growth hormone deficiency. In addition, while testosterone was not proven to hold direct consequences to height, the correlation between height and higher testosterone production is a subject to be studied and may prove to be very important to this review.

To conclude, this study has shown that the benefits of strength training, including increased production of growth hormones, improvements in bone density, increases in muscle strength, and boosts in self-esteem, outweighs the plausible risks like injury to growth plates, etc. Moreover, these risks can be avoided most of the times by using the appropriate amounts of weights, proper technique, and professional supervision to train.

Table 1 summarizes the benefits and risks, as well as the specific conditions to follow in order to reduce the risk of injury. Although genetics is the primary determinant in the peak stature of a child, the conditioning of the growing body during this crucial period is just as important as one fault physical activity, such as strength training, could

potentially alter their linear growth curve and final height. However, following the listed conditions suggested in this study, any concerns of strength training negatively impacting children and adolescents should be dispelled. Any possible injuries or negative effects observed by exercise should be anticipated and one should take full responsibility regarding the plausible risks that may be pertinent to physical growth.

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# Applying Constructivism in Neurodiverse Classrooms

Seoyoon Eunie Choi

Seoul International School, Republic of Korea

choieunie@gmail.com

## Abstract

Cognitive development theories differ on how young students can meaningfully process new information and retain that information for future knowledge-building through scaffolding within their zone of proximal development. More traditional theories like the cognitive load theory adhere to the rote memorization approach by categorizing students as passive learners and the teachers as initiators who provide information in a structured, often rigid format, to be stored and retrieved for future application using their working memory. In contrast, the more progressive theories, like constructivism, are premised on the belief that students should proactively initiate their own learning while teachers act more as facilitators. The current trend in government policy under ESSA is to embrace the latter approach in the classroom, which is also more inclusive of all types of students, especially neurodiverse students. Moreover, teachers can utilize the wider range of assistive technology tools to accommodate and support their students' unique learning styles.

*Keywords: learning, constructivism, cognitive load theory, zone of proximal development, assistive technology*

## Introduction

When children struggle academically in the classroom, the traditional recourse may have been to address their needs for support by classifying them as limited in intelligence and capability before placing them in special

education classrooms under the presumption that they would hold back the rest of the class in a regular classroom setting [1]. However, the more progressive pedagogical approach is to integrate these students, recognizing them as equally valuable and beneficial to a dynamic classroom environment. They may have different methods of learning, as well as their own challenges, but their unique set of circumstances can be overcome with the right accommodations and support.

Constructivism is a theory that allows these types of students flexibility in their mode of learning rather than forcing them to abide by a rigid set of expectations which may not be effective or in alignment with their learning style [2]. This theory, along with the more traditional teaching theory known as cognitive load theory, will be explained and discussed in detail in this paper. In addition, the paper will delineate how educators can implement effective teaching strategies in their classrooms, especially with the increasing availability of more advanced assistive technology to support students with varying academic and intellectual needs.

## Constructivism, Cognitive Load Theory, and the Zone of Proximal Development

To implement a more effective instructional design in alignment with the cognitive development of young students, one must consider the leading theories on how they process new information. Cognitive Load Theory asserts that cognitive functions, such as short-term and long-term memory, are essential

considerations of instructional design [2]. The theory is, in part, based on evolutionary educational psychology which posits that processing biologically secondary knowledge mimics the architecture of biological evolution [3]. Specifically, while biological primary knowledge such as language skills are naturally acquired, biological secondary knowledge is acquired through problem-solving, reading, listening, and researching in a more structured educational setting. Writing, science, and math also fall within this latter category [2].

Before secondary knowledge can become part of one's general knowledge base, the information must first be organized in the working memory, also known as 'short-term' memory, which is limited in capacity and duration. Once the information is acquired and interpreted, it can be stored in the long-term memory, which has much greater capacity [4]. For example, in the process of reading, knowledge stored in the long-term memory region can be retrieved as working memory in order to generate an action. In other words, the knowledge of how to read, which is stored in the long-term memory of a literate individual, may be brought back as working memory to function together with the new information to facilitate learning [4]. Moreover, although working memory is limited when working with new information, it is not when working with information previously learned and processed before being stored in one's long-term memory [4].

Based on cognitive load theory, building a breadth of information stored in long-term memory can be efficiently achieved through a commonly practiced teaching method called the "worked example effect" [2]. This approach encourages showing a learner an example of the completed work before asking them to perform the task. Studies have proven this method to be effective in improving student performance [2]. The rationale for this method is that a "worked example" reduces the workload of the working memory, because it eliminates possible alternative actions. With more "worked

examples" stored in the long-term memory, students can learn to develop solutions based on previous "worked examples" and think deeper by themselves. Essentially, to formulate better solutions while processing new information, general knowledge acquired from previous learning, including from worked examples, must be stored in the long-term memory [2].

Over the years, cognitive load-based approaches have been criticized as ineffective in teaching students to self-monitor or self-regulate [5]. Specifically, some cognitive development theorists believe that self-regulation should be cultivated in a learning environment in which students have more autonomy and are encouraged to be proactive in acquiring knowledge. They argue that self-generated thoughts, feelings, and behaviors can be channeled to attain desired goals, thereby increasing self-satisfaction and sustained motivation [5].

Applying this cognitive development theory to the classroom setting, constructivists advocate that teachers should foster a deep and meaningful learning environment in which the students develop their critical thinking skills [6]. Constructivist approaches, which recognize the interplay of individuals with their environments, were first applied in classrooms as early as the 1960s [7]. Jean Piaget, a Swiss psychologist, was one of the first people to develop the idea of constructivism [7]. Piaget's theories, especially those related to the early years of development, are still used today, such as the idea that as neurotypical children (children without clear developmental disorders or drawbacks) grow, they reach milestones at certain ages [7]. These approaches are used in teaching institutions across the world in a wide range of subjects such as math, science, and humanities.

The constructivist method usually calls for more group work, as students are encouraged to critique each others' ideas and answers while working together to solve problems in experiments and projects [6]. Allowing students to work at their own pace and learn with their own

understanding of things creates a more flexible learning curriculum than would be likely if all subjects were taught through a single method from one teacher. Research shows that constructivism promotes creativity and engagement in students, although many different contextual factors and individual personality traits, as well as learning abilities, must also be considered [8].

Lev Vygotsky, a psychologist from the same era as Jean Piaget, posited a similar theory about the cognitive development of children. Vygotsky, however, placed greater emphasis on the importance of societal and cultural impacts. He argued that social interaction is the most essential component of learning and development and that biological development and environmental factors conjointly affect learning outcomes. His social theory consists of three principles: (1) social interaction plays a key role in the acquisition of knowledge, (2) some aspects of cognitive development are limited to a specific developmental periods, and (3) that the process rather than the product of learning must be assessed for humans to fully learn and understand [7] [9].

Vygotsky furthered Piaget's theory by classifying all tasks into three categories: (1) those we can do by ourselves, (2) those we can do with guidance, and (3) those we cannot do at all [9]. The first and third categories are not particularly helpful to learning, as doing something one is already good at does not help them develop, and attempting something that is too advanced or unfamiliar for a particular age will be too frustrating to facilitate learning [9]. For example, assigning basic addition tasks to an average high schooler would be pointless, just as a kindergartener should not be attempting calculus without having first mastered basic addition. Instead, the focus of learning should fall within the second category wherein students attempt things that they can do with some guidance.

In developmental psychology, the second category, where most learning occurs, is called

the zone of proximal development [4] [9]. This zone can be applied in a wide range of subjects, from mathematical calculations to daily problem solving, to aid a child's cognitive development. The zone itself is essentially the gap between a learner's task completion level and their potential for task completion under guidance. Vygotsky's contention was that the potential for future development, and not a simple evaluation of task completion, is crucial for assessing and promoting cognitive development [7] [9].

Similar to Vygotsky's zone of proximal development, scaffolding refers to interactive instructional relationships between teachers and their students that enables students to solve problems beyond their unassisted efforts [4] [10]. Scaffolding involves providing assistance to students only upon reaching the upper threshold of their respective zones of proximal development. Through scaffolding, students learn new skills or concepts, which culminates in completing a task successfully, ultimately reaching autonomy via a gradual transfer of knowledge or learning strategies from the teacher to the student [10].

### **Constructivism, Cognitive Load Theory, and the Zone of Proximal Development**

Over the years, constructivism has moved from research into classroom application. Traditionally, too much emphasis was placed on curriculum and not on student thinking, which discouraged viewing students as original thinkers with opinions about the emerging world around them [11]. While some may argue that explicit instructions better serve neurodivergent students, others have promoted constructivist strategies that encourage students to develop ideas by collaborating with their teachers and peers [6]. Constructivism has also helped bridge the learning gap in inclusive classrooms by assisting a student with special needs with active participation and learning tailored to the student's own learning characteristics, the task at hand, and contents that are already familiar to the student [12].

Since constructivism is based on the notion that people acquire knowledge by constructing their own understanding of the world around them, it prioritizes student-dominated learning and interaction [4]. However, teachers in the classroom still play a critical role as facilitators rather than information conduits. As facilitators, teachers must show students scaffolding techniques through which they can connect their past experiences to new information, thereby enhancing their knowledge [6]. Moreover, with careful design appropriate technology tools can provide additional assistance in supporting the students' learning especially in neurodiverse classroom settings [6].

Constructivist classrooms emphasize real-life problem-solving, problem-based learning (PBL), independent investigation, the pursuit of personal interests, simulation, discussion-collaborative learning, think-pair-share, and the utilization of higher-order thinking skills [14]. Constructivism is based on the idea that everyone, whether neurotypical or with special needs, learns differently. Therefore, student-centric learning can allow all students to build their own ideas and learn in their own ways. Others believe that constructivism can help students with neurological conditions such as ADHD, bipolar disorder, or fetal alcohol spectrum disorder because it allows them to pace the lessons themselves and still learn alongside their peers [12].

In this spirit, the Every Student Succeeds Act (ESSA) replaced No Child Left Behind as the national educational policy in 2015. ESSA states that the Individualized Educational Plan (IEP) team determines when a student with a significant cognitive disability should be evaluated under an alternative assessment standard so long as the determination is consistent with guidelines established by the state (Section 1111(b)(2)(D)(ii)(I)). ESSA applies more constructivist approaches to both assessment and instructional design, even permitting the use of assistive technology when appropriate, especially for students experiencing learning disabilities or

neurodivergence. Despite these potential benefits, some argue against constructivist approaches in teaching because tailoring lessons to accommodate each student may be time-consuming and inefficient [13].

### **Working Memory of Neurodivergent Students**

Working memory is a basic mental skill which allows the brain to hold information in the short term, thereby facilitating learning and completion of tasks. Moreover, new information once acquired can be stored in long term memory but potentially retrieved as working memory when the need arises again in the future [2] [3]. Children with learning difficulties such as ADHD or those with other executive function disorders who are neurodivergent may struggle to utilize this brain function and to perform everyday tasks [17].

One challenge that neurodiversity presents when being applied to autism is the fact that autism encompasses a wide range of learning disabilities that presents a multitude of different circumstances and challenges [18]. Further exploration is needed regarding how to address some of these learning challenges such as assisting in developing one's working memory in the classroom and beyond.

The ability to use working memory is especially important for young children in school because working memory is needed when performing tasks such as mental math, including helping children to visualize numbers and to apply mathematical functions in their heads [17]. Children working memory deficits have difficulty picturing numbers and holding them in their working memory order mentally manipulate them and produce correct answers. Working memory deficits may also hinder children's performance of physical tasks, as they may not remember in which order the tasks must be completed, or they may not be able to make sense of the instructions they are provided [19].

Children who appear to have working memory deficits may instead have attentional deficits [20]. In other words, rather than having difficulty holding the information in mind, the child may have initial difficulty paying attention to the

instructions provided. It is worth noting that in the past few decades, studies indicate that many disorders of the brain or mind are not without benefits. For example, those diagnosed with autism spectrum disorder (ASD) appear to have strengths working with systems and identifying tiny details in complex patterns just as those with dyslexia seem to perceive peripheral or diffused visual information more quickly than neurotypical individuals [15]. Given such varied presentations and capacities, a full evaluation of a child's cognitive abilities may help uncover the factors involved in their academic difficulties [21]. This improved understanding may help assist educators in determining what, if any, assistive technologies may be effective in addressing the student's individual learning style.

### **Importance of Assistive technology in New Education Policy**

Assistive technology refers to any technological device, item, piece of equipment, or product system that improves the functional capabilities of individuals with disabilities in bolstering their cognitive skills as well as in maximizing their attention span and time management [22]. Assistive technology may be viewed as more appropriate for low-functioning students, especially when mainstreaming them for social reasons, but high-functioning, learning-disabled students may benefit from such academic support as well [22].

To manage tasks and succeed in goal-directed activities, students need to have a wide range of executive skills, which consist of metacognition, appropriate behavior and actions, mental shifting, and sustained attention. When these executive functions are weak or lacking, the student can be hindered academically [23]. In order to reduce such obstacles, various assistive technologies may be employed to help meet each student's individualized needs. For example, for students who struggle with self-control, Book Creator, a software application, helps students with self-management in social situations [24]. In addition, the Self-Management Checklist Maker is

a website that teachers can use to monitor their students, and which, in turn, can aid the student [24].

Low-tech prioritizing strategies, reflective journaling, and capturing thinking can help students develop their metacognition skills. Capturing thinking can be done through the utilization of technologies such as the SmartPen or AudioNote app, both of which record students as they talk to themselves through an activity or assignment [25].

Cognitive flexibility, shifting, and organization manifest in the student's ability to follow a schedule and make connections across situations. These skills can be aided with technology such as Choiceworks, First-Then Visual Schedule, Time-Timer, and Wunderlist to help students manage time and make sure not to get lost throughout the day. Similar to scheduling, goal-directed persistence--the students' ability to maintain their focus to accomplish a goal--can be extremely difficult for some, especially if they struggle to follow a schedule [24]. Goal-directed persistence can be aided with simple things such as calendars, checklists, and data chart organizers [24].

One effective strategy teachers use to jog students' working memory is the KWL (Know Want Learn) activity before introducing new but related information [25]. Another form of assistive technology can be software applications like graphic organizers or other visual aids like slides and flashcards used to further support learning. Moreover, websites like Khan Academy provide user-friendly tutorials online about multiple subjects.

While these learning tools assist students in the classroom, neurodiverse students also need social and emotional support. Despite the wide range of assistive technology available today, one of the most important factors in the successful mainstreaming of neurodiverse students is dependent on the positive attitude projected by the classroom teacher [28]. Hence, the teacher still plays a significant role by reinforcing the belief that the neurodiverse

students are actually adding value to the classroom.

## Conclusion

In recent years, appreciation for active learning through constructivism, wherein students acquire and process new information, has drawn attention to the importance of including and embracing neurodiverse students in the classroom. In the past, learning processes such as cognitive load theory expected students to simply absorb information instead of taking a more proactive role. Constructivism's broader acceptance has encouraged children to take greater initiative in the learning process, while teachers serve as facilitators rather than rote pedagogues. This approach can be more beneficial to neurodiverse students because students can tailor their learning experience to what fits them, rather than attempting to learn through more rigidly structured methods. This cultural shift in learning may fundamentally change the structure of classrooms in the future.

More traditional, rigid learning models required students to absorb information as passive learners. Those who could not process the information readily were often placed in special education classes, in part because classroom teachers could not accommodate the unique learning styles of every student in their class. However, with the growing acceptance of constructivism, more educators are implementing student-led learning while utilizing advances in assistive technology. While educators recognize the importance of mainstreaming some neurodiverse students, teachers continue to play a critical role in supporting students socially and academically regardless of neurocognitive status. Teachers are indisputably vital to the learning process, even in constructivist classrooms.

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# Brain Reactions to Film Watching

Audrey Czarnecki

Thomas Jefferson High School for Science and Technology, United States  
audreyc947@hotmail.com

## Abstract

This systematic review sought to uncover the mechanisms through which films induce certain emotions and the ways in which people's brains respond to those stimuli through the lens of neuroscience. Films vary in composition, though many make use of motion, both through characters and the camera, to elicit emotions. They also use previously successful scene setups and actor castings for a similar effect. Brain regions have differential reactions to films, especially in response to film duration, category, and context. Brain hemispheres generally differ from each other in their responses as well, such as in response to positive versus negative stimuli. People's characteristics, such as empathy levels and age, can also influence the level to which the brain responds to films and the differences between activation levels of different regions. Substance abuse alters the brain's chemistry; it can also increase the activation of specific brain regions. Several studies utilize electroencephalography and functional magnetic resonance imaging; their limitations are discussed. Future research could also explore other possible measures of emotional response to films.

*Keywords: Emotional induction, Film, Movie, Brain regions*

## Introduction

Countless films have been produced since cinema began in the late 1800s (O'brien, 2015). There are several genres, production companies, and distributors that are well-known to the public,

with respective examples being fantasy, the Walt Disney Studios, and Columbia Pictures. Another familiar aspect of films is their ability to elicit certain emotions at specific times. People might cry, laugh, feel anger, or feel frightened, depending on the scene. Their facial expressions might also change unintentionally (Fanti et al., 2015). There are databases containing films meant to induce particular emotions, though it is not always specified how those films successfully complete the task, and some studies partly or mostly base the effectiveness of the films on ratings from their participants (Gabel et al., 2019; Zupan & Eskritt, 2020). This review attempts to uncover the ways in which films influence people's emotions and affect the brain.

## Methods

A systematic review was conducted by searching the PubMed database for papers on emotional induction through films. Two separate searches were completed with the following phrases: "film' and 'emotion'" and "'movie' and 'emotion.'" A total of (n = 696) papers were present at the start of the review. Date of publication and location of research were not of concern to this review and no papers were excluded based on these criteria. The titles of the papers were reviewed manually. Any paper not pertaining to films affecting emotions or the way in which the brain processes emotions was excluded. After this first screening, (n = 223) papers remained. Another group of (n = 88) papers was removed because they contained neither the word "film" nor the word "movie" in their titles. There were (n = 12) duplicates, which were also removed. The abstracts of the

remaining (n = 123) papers were downloaded and individually reviewed for relevance. Papers were removed if they only spoke of creating a database of films for eliciting certain emotions without giving concrete data for their effectiveness or if they did not focus on cerebral responses to films. Afterwards, (n = 26) papers remained. An attempt was made to retrieve the full text for each paper, but (n = 3) were unavailable. After screening the full texts of the papers, (n = 16) were included in the review. Figure 1 depicts the overall screening process.

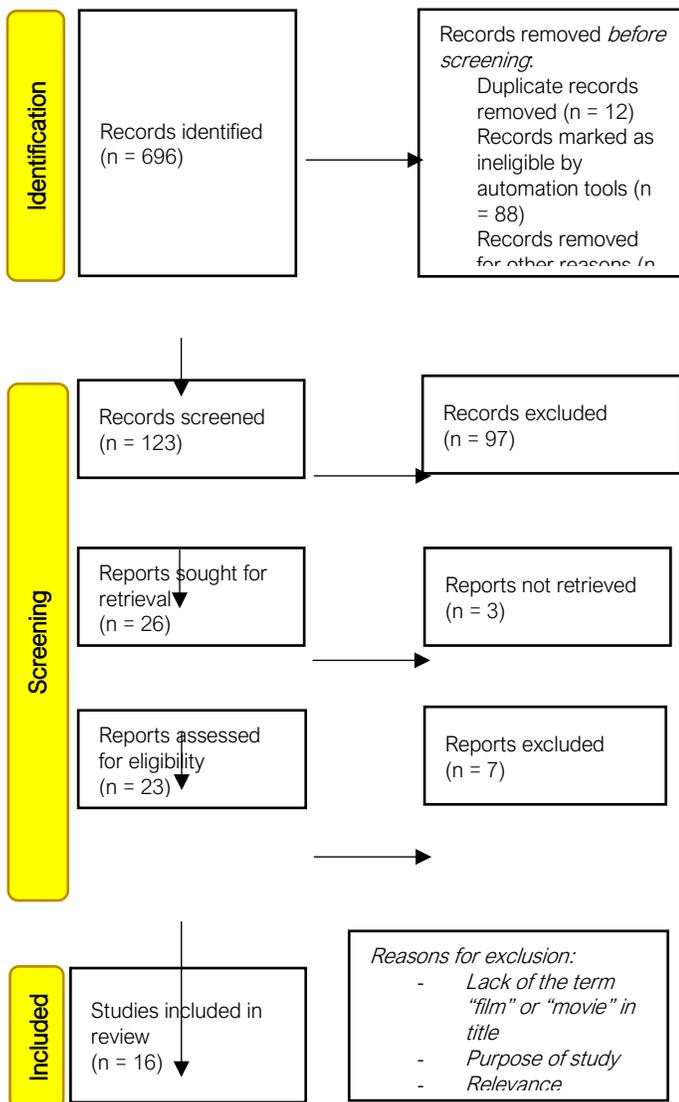


FIGURE 1: PRISMA flow diagram depicting the process for choosing the papers included in the review.

## Film Techniques for Influencing Emotions

One of several ways in which films may emotions is through the use of motion (Dayan et al., 2018). Local motion concerns the movement of objects and humans whereas global motion concerns the camera. The latter tends to influence emotion more strongly than the former. Motion can convey information that might describe the emotions of characters, the movement of the plot, or other key factors that play in a film's storytelling, thus influencing the viewer (Dayan et al., 2018).

Once a particular setup has been used and is deemed effective, it tends to show up again in future films. For instance, several films depict romantic separation scenes by using a couple standing together, some close-ups, the physical separation of the couple, and a crescendo of sad music (Schlochtermeyer et al., 2017). The use of certain actors can also influence people's emotions. Zhu & Wu (2021) found that people were more willing to watch films with skilled actors (those with recognized acting abilities) than publicity actors (those chosen based on their physical appearance) and that they were more engaged emotionally when skilled actors were present.

## Brain Reactions to Films

### *Brain regions and chemical secretions*

The brain is composed of several regions, such as the dorsal anterior cingulate cortex and the dorsomedial prefrontal cortex, which communicate with each other and have different functions (Anderson et al., 2013), although many be activated in conjunction to process stimuli from films (Karama et al., 2011). Several experiments show the diversity of brain regions that are involved in the processing of audiovisual information and the emotions that come with them. Schlochtermeyer et al. (2017) used functional magnetic resonance imaging (fMRI) in order to determine anterior and posterior cortical responses to sad romantic separation scenes. Three forms of the scene were used: one was the original scene from the film, one had a replaced

segment, and one had a random order. The anterior and posterior cortical midline regions were activated more when presented with the original scene and the scene with the replaced segment while the temporal gyri were activated less. The anterior and posterior cortical midline regions are part of the default mode network, which is associated with intrinsic processing, while the temporal gyri process external stimuli, such as sound (Schlochtermeyer et al., 2017). Longer scenes also promote greater activation of brain regions (Schlochtermeyer et al., 2017). In another study, global motion in emotional film clips revealed significantly stronger blood oxygenation level dependent responses to emotional relative to neutral clips of regions like the right inferior frontal gyrus, right precuneus, and left inferior occipital gyrus (Dayan et al., 2018).

Different brain regions are activated in response to different stimuli. For instance, traumatic films tend to activate fear processing regions of the brain, such as the amygdala and insula, and activation of those regions can be influenced by the production of hormones in the endocrine system (Miedl et al., 2018). Amusing films activate the temporal cortex and bilateral temporo-parieto-occipital cortex whereas erotic films activate areas like the amygdala and prefrontal cortex (Karama et al., 2011). Domain-general brain networks can also work together to promote different emotional outputs. One finding from Raz et al. (2016) was that stronger connectivity between the dorsal salience network and medial amygdala network was associated with greater emotional ratings in all film categories (anger, fear, and sadness) examined.

### *Hemisphere asymmetry*

Several papers discussed whether there is a difference between the left and right hemispheres in the processing of films and emotions. Two stated that the effects are not different between the two hemispheres (Dennis & Solomon, 2010; Kaviani et al., 2010), while three did find differences (Costa et al., 2006; Tomarken

et al., 1990; Wittling & Pflüger, 1990), which are summarized in Figure 2. Costa et al. (2006) found differences in the electroencephalographic (EEG) synchronization of different brain regions. For instance, sadness was more synchronized in the left while happiness was more synchronized in the right hemisphere (Costa et al., 2006). Wittling & Pflüger (1990) found that the right hemisphere had more control over cortisol secretion compared to the left hemisphere. Tomarken et al. (1990) showed that frontal asymmetry was associated with increased differences in positive and negative reactions. Other research seems mainly to back up the claim that the brain hemispheres do differ in their responses to stimuli, such as by controlling the heart during film watching (Wittling et al., 1998) or by influencing response inhibition to different faces (Schrammen et al., 2020).

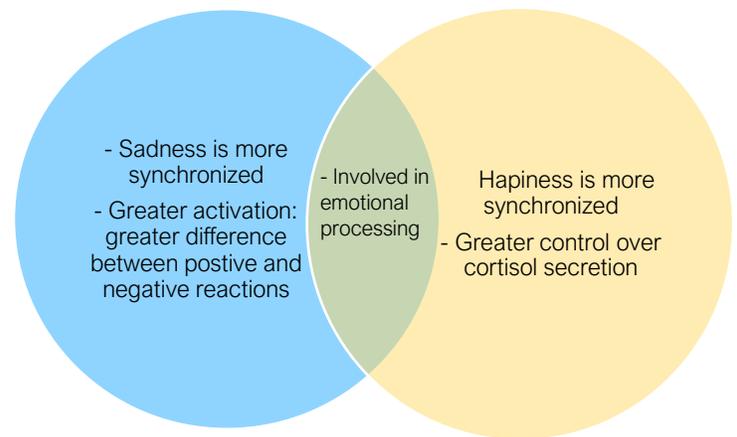


FIGURE 2: Venn diagram comparing the two hemispheres of the brain.

### *EEG findings*

Electroencephalography can be used in order to measure electrical brain activity with electrodes (Müller-putz, 2020). Particular frequencies correspond to different mental states and functioning of different brain regions (Krause et al., 2000). For instance, Krause et al. (2000) found that there was greater synchronization

while watching aggressive versus sad and neutral films in the 4-6 Hz band, which might reflect theta EEG activity and activation of hippocampal-cortical pathways. One finding from Costa et al. (2006) was that frontal regions were more synchronized than others and that sadness was more synchronized than happiness.

#### *Physical measure of attentiveness*

Some automatic physical processes, such as blinking, can reflect the brain's response to external stimuli. Having greater blink rate inhibition reflects greater attention to visual stimuli so less information is lost. In a study conducted by Maffei & Angrilli (2019), it was found that people blink less while watching films containing erotic, scenic, or compassionate elements, whereas they blink more while watching films containing threatening elements that elicit fear and sad elements. The erotic and scenery categories in the study were rated as the most pleasant, therefore it follows that people would pay more attention to them and blink less often. Compassion clips were rated as unpleasant, but they contained prosocial elements that would move the viewer to want to help the characters. Fear and sadness clips made people want to reject the information and formulate a plan for defense.

#### *Personal characteristics affect emotional responses to films*

People with certain personality traits, such as different levels of empathy, can have different neural responses to films. A study by Maffei et al. (2019) shows that higher levels of empathy are associated with greater activation of brain regions involved in the processing of other people's pain and greater cortical gamma secretion in response to several film categories whereas lower levels of empathy are associated only with an increase in cortical gamma secretion in response to negative films. A survival instinct is activated by the negative films while other films presenting appetitive material may be less arousing because

they are not as ingrained biologically (Maffei et al., 2019).

People with substance abuse disorder have different activation of brain regions in response to films. Park et al. (2016) explored the effects of alcohol dependency on the experience of anger through fMRI scans. Alcohol-dependent and non-alcohol-dependent participants were found to experience anger to a similar extent, though the alcohol-dependent group had significantly greater activation of the bilateral dorsal anterior cingulate cortex, right cuneus, and right precentral gyrus.

Age has also been shown to impact emotional responses, especially since the brain is constantly changing and developing as people grow up. Gruskin et al. (2020) found that children's brain responses were unrelated to depressive symptom severity whereas adolescents with greater depressive symptom severity had atypical fMRIs.

#### **Discussion**

Films may use various techniques in order to elicit specific emotional responses, such as by utilizing motion to convey information, making use of previously successful setups, and using well-known actors. As the brain is composed of several regions, there is differential activation of those regions based on film category, presented context, and the length of the film, and some regions may be activated together to generate the appropriate emotional response. The amygdala is frequently mentioned in studies of emotional processing as it is generally associated with the processing of fear- and anxiety-inducing stimuli (Davis, 1992).

It is likely that the left and right hemispheres of the brain react to stimuli in different ways as evidenced by studies specifically based on films and studies based on other things like facial expressions. EEG studies also showed the different amounts of synchronization in response to different film categories, thus confirming that different brain regions react to different film categories.

Spontaneous blink rate demonstrates a level of attention, and it generally increases when a person is presented with unpleasant and threatening information while it decreases when there is pleasant imagery or a need for greater analysis of scenes.

Having higher levels of empathy is generally associated with greater activation of pain-processing brain regions and greater cortical gamma secretion compared to people with lower levels of empathy. Substance abuse and age also influence the brain. The former increases activation of specific brain regions, whereas the latter changes the relation between depressive symptoms and brain responses. Other personality traits and mental conditions likely influence the brain's responses to films as well.

### *Limitations*

As this study was conducted under a time constraint, it was difficult to perform multiple searches, thus there was a limited number of papers to review. The researcher looked through all of the papers, so there was also a limit to the number of papers that could be read. Some full-text papers could not be accessed because of paywalls and other obstacles. There could also be a lack of research in some areas of how films elicit certain emotional. The majority of papers included in this study discussed the responses of specific brain regions and differences between them, but only Dayan et al. (2018), Schlochtermeyer et al. (2017), and Zhu & Wu (2021) described some of the mechanisms behind how films can influence audiences.

Another limitation could come from the methods of the papers included in this study. EEGs can only detect synchronous brain activity at the scalp, so some information might be lost (Müller-putz, 2020). Neither EEGs nor fMRIs are invasive, which means that both are indirect measures of brain activity, and their findings rely on inferences (Hall et al., 2014). The findings from these studies might not be conclusive because of unknown confounding factors and the limitations of non-invasive technology.

There were also limitations to the selection criteria. The researcher only included papers with the word "film" or "movie" in the title, which might have eliminated papers of interest. The papers included mainly analyzed people's emotions in response to film clips or scenes rather than full films, which could impact emotions and brain regions.

### *Future research*

Future research could take into account other physiological responses people might have to films, such as salivary cortisol levels, heart rate, and skin conductance levels. Other databases, such as EBSCO, JSTOR, and ProQuest, and other keywords could be used to obtain a greater variety of papers and information. More specific searches could be conducted to find other ways in which films induce specific emotional responses. Searches could also be conducted on the influence of mental conditions on the emotional reception of films.

### **Conclusion**

In conclusion, films employ various methods that are translated into differential activations of brain regions, including the left and right hemispheres, and brain responses can be influenced by a person's characteristics and substance use. Films are often used as a source of enjoyment, but many neural processes are involved in generating the specific emotions felt while watching films. They can be a source of inspiration and can be used for scientific experiments.

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# Exploring the effect of music therapy in elders living in hospice and palliative care

Annesha Dey

Dougherty Valley High School

deyannesha22@gmail.com

## Abstract

Music therapy is often used in hospice and palliative care of elderly adults and senior citizens nearing the end of their lives. This article discusses the benefits of various types of music therapies in elderly care treatment, including group music therapy (GMT), recreational choir singing (RCS), learning to play an instrument, and musical relaxation techniques. However, though music therapy is being used with increasing frequency in the treatment of those with terminal illnesses, due to the lack of empirical data in the field, many are skeptical of whether external musical therapy can medically improve the condition of terminally ill patients and elders. Thus, this article will also focus on determining the extent to which music therapy improves the mental/physical health and condition of elders living in hospice and palliative care, using existing empirical studies that document evidence-based data. Conclusions establish that though music therapy does not improve the physical condition of terminally ill elders to a significant extent, it does increase their quality of life and mental health in their final days. It further establishes that long-term music therapy and repeated sessions are highly beneficial in hospice and palliative care of elders.

*Keywords: music therapy, palliative care, hospice care*

## Introduction

Music therapy is the clinical use of music interventions that have been shown to provide therapeutic benefits to those living with terminal

illnesses (O'Callaghan C., 2001). Music therapy is an established allied health profession, and music therapists are Board Certified (MT-BC) by the Certification Board for Music Therapists (CBMT) upon the completion of an undergraduate degree and internships/examinations (Mandel S.E., 1993). They help address a variety of healthcare goals, including promoting overall wellness, managing stress, treating memory care patients, promoting physical rehabilitation, etc. (Amy Clements-Cortes, 2004). In elderly hospice/palliative care, musical therapies are offered in various forms; a few of which will be discussed below in addition to the benefits of each.

### *Dalcroze Method*

This method emphasizes the power of physical movement, which therapists typically use to improve physical awareness in patients with significant motor difficulties. It focuses on rhythm, structure, and movement expression, bringing hospice elders to higher levels of musical understanding and movement. Applications of this method include teaching elders how to play musical instruments (Salmon, 1993).

### *Neurologic Music Therapy (NMT)*

This model of music therapy is based on neuroscience and emphasizes the influence of musical perception/production on the brain's functions and behaviors. It is used to instigate brain changes in a patient, for example, training motor responses, etc. Applications of this therapy

include listening to live or recorded relaxing music daily (Starr, 1999).

### *Group Music Therapy (GMT)*

GMT is offered by a music therapist and may offer a variety of activities like listening to music, singing, and playing instruments. Emotional processing, which refers to the use of musical interactions to aid in self-reflection, is present in GMT participants (Demmer & Sauer, 2002). This kind of emotional processing may be associated with improved moods and lower rates of depression in older adults. GMT offers social interaction; for example, the one-to-one relationships between group members and the therapist (Gold et al., 2019)

### *Recreational Choir Singing (RCS)*

RCS is typically facilitated by some sort of choir leader and focuses mainly on singing. Cognitive processing, or the learning/memorizing of music pieces, is highly present in RCS. This kind of cognitive processing may maintain cognitive functioning in older adults, specifically those with underlying disorders like dementia. RCS additionally reinforces key social mechanisms; for example, a shared sense of mastery/achievement through group performances of musical pieces (Gold et al., 2019).

### *Study objectives*

1. Determine the extent to which music therapy improves the physical condition of elderly hospice/palliative care patients.
2. Determine the extent to which music therapy improves the length and quality of life of elderly hospice/palliative care patients.
3. Determine the extent to which music therapy improves the mental health of elderly hospice/palliative care patients.
4. Determine the extent to which music therapy improves a diagnosed condition like dementia, or reduces the risk of its onset.

## **Methods**

Data from this study comes from ten existing evidence-based studies either published in scholarly journals, or unpublished master's theses. Organized chronologically by date (1993-2019), studies were chosen based on objectives/variables regarding mental and physical health of patients receiving musical therapy. Exclusion criteria is age; all subjects are above 65 years of age. Each study addresses 1 or more objectives listed above: physical condition, quality of life, mental health, or improvement/prevention of diagnosis. This paper will discuss each study's findings and use them to conclude the overall effectiveness of music therapies on elders in hospice/palliative care.

## **Results**

*Study 1:* Calovini's master thesis on the effect of participation in one music therapy session on state anxiety in hospice patients (Calovini, 1993). 11 adult subjects were observed over the course of 4 months, with eight subjects having been receiving music therapy before the study. All subjects had been diagnosed with some sort of terminal illness. Music therapy was offered through listening and singing along to music, learning to play an instrument, or relaxing with music; each subject was given the option to choose a specific type of therapy. The study utilized various measurements for anxiety, the methods and results of which are listed below:

1. Spielberger's State-Trait Anxiety Inventory (STAI) self-reporting questionnaire; data showed no statistically significant differences before and after music therapy sessions
2. Physiological measures (systolic/diastolic blood pressure, pulse rate, finger temperature); data showed no statistically significant differences before and after music therapy sessions (Hilliard 2005).

*Study 2:* Longfield's study on the effects of music therapy on pain and mood in hospice patients (Longfield, 1995).

This quasi-experimental study utilized eight adult subjects in hospice care, all diagnosed with terminal cancer. They received music therapy via taped recordings that they listened to through headsets, for 45 minutes a day for five days. Inferential statistics were used to compare the data difference between pre-test and post-test conditions. The data collection methods and results are listed below:

1. Short-Form McGill Pain Questionnaire (SFMPQ)- data showed a statistically significant decrease ( $P < 0.001$ ) in pain
2. Linear Analog Self-Assessment Scale (LASA)- scores showed a statistically significant increase in mood from fatigueness and anxiety.

*Study 3:* Krout's study on the effect of single-session music therapy interventions on observed and self-reported levels of pain control, physical comfort, and relaxation of hospice patients (Krout, 2001).

90 total sessions were conducted with a total of 80 subjects from Hospice of Palm Beach County, Florida. Five board-certified music therapists provided live music therapy services on a regular schedule. Listed below is the methods of data collection and results regarding patients' levels of pain control, physical comfort, and relaxation before and after each music therapy session:

1. Independent observation- used one-tailed t tests; data analysis revealed a significant difference ( $P \leq 0.001$ ) for changes in the three dependent variables before and after music sessions.
2. Self-reporting: data analysis showed a significant difference ( $P \leq 0.005$ ) in the three dependent variables (Hilliard, 2005).

*Study 4:* Wlodarczyk's study on the effect of music therapy on the spirituality of persons in an in-

patient hospice unit as measured by self-report (Wlodarczyk, 2003)

10 newly admitted adults ( $n=10$ ), diagnosis, age, or religious preference, participated in this study and had to complete a questionnaire. There were two sessions, A (cognitive-behavioral music therapy) and B (non-music visit). The sessions operated in a 30-minute ABAB pattern for half the participants, and BABA pattern for the other half. The data collection methods and results are listed below:

1. Spiritual Well-Being Scale (SWBS)- 18 item questionnaire to measure spirituality; statistical analyses indicated a significant increase in spirituality during music sessions.

*Study 5:* Hilliard's study on the effects of music therapy on the quality, length of life, and time of death in relation to the last visit of terminal cancer hospice patients (Hilliard, 2003).

In a randomized clinical trial, a total of 80 subjects ( $n=80$ ) participated in the study and were randomly assigned to either of the two groups: (i) an experimental (receiving routine hospice services and clinical music therapy) or (ii) control (receiving routine hospice services only) group. The study controlled the place of residence to hospice homes, and matched equal numbers of genders and ages to each group. Listed below is the methods of data collection and results regarding patients' length and quality of life, and time of death in relation to the last visit (because music therapists often report that music assists the dying in releasing life):

1. Hospice Quality-of-Life Index (HQOLI)- 29-question self-report used to measure changes in quality of life; results showed a significant difference for quality of life for patients receiving music therapy.
2. Hospice discipline (nurse, music therapist, etc.)- evaluated time of death relative to the last visit; results showed no statistically significant difference.

Medical record analysis- used to measure length of life; following the subjects' deaths,

with the Hospice Management Systems-Plus software, results showed a statistically significant difference between control and experimental group (Gallagher & Steele, 2001).

*Study 6:* Takahashi study on the long-term effects of music therapy on elderly with moderate/severe dementia (Takahashi et. al, 2006).

Over the period of 2 years, the long-term effects of a weekly group music therapy on the elderly with moderate or severe dementia was assessed. It was determined by observing changes in the cortisol level in saliva, blood pressure, and by an intelligence assessment. Results from a music therapy group were compared with that of a non-music therapy group. Listed below are the observed the results regarding patients' improvement in dementia:

1. Systolic blood pressure determined 1 and 2 years after the start of therapy increased significantly in the non-music therapy group compared with the music therapy group ( $p < 0.05$ ).
2. No significant differences in cortisol level in saliva or intelligence assessment score were observed, but the music therapy group maintained their physical and mental states better than the non-music therapy group during the 2-year period. Results show the lasting effect of continuous music therapy

*Study 7:* Verghese's study on the effect of leisure activities such as musical therapy and dancing on the risk of dementia in the elderly (Verghese et. al, 2014).

In a prospective cohort of 469 subjects older than 75 years of age who did not have dementia at baseline, cognitive and physical activity was observed using a scale that used activity-days per week as units of measure. Over a median follow-up period of 5.1 years, dementia developed in 124 subjects, Alzheimer's in 61 subjects, vascular dementia in 30, mixed dementia in 25, and other types of dementia in 8. Listed below are the

methods and results regarding the effect of musical activities on the onset of dementia:

1. A one point increment in the cognitive-activity score was associated with a reduced risk of dementia. This association between cognitive activity and decreased risk of dementia was persistent after the exclusion of subjects with preclinical dementia at baseline. Results were similar for Alzheimer's disease and vascular dementia. Increased participation in cognitive activities showed reduced rate of memory decline over the observation period as well.

*Study 8:* Särkämö's study on the effects of music therapy on the improvement of mental functions in patients with mild-moderate Dementia (Särkämö et. al, 2014).

In a randomized clinical trial, participants with mild-moderate dementia were randomly assigned to a singing group (SG), music listening group (MLG), and a usual care control group. They engaged in this group-based music program for weekly 1.5 hour sessions over the course of 10 weeks. Listed below is the results regarding patients' improvement of mental abilities:

1. SG and MLG improved mood, orientation, remote episodic memory, attention, executive function, and general condition.
2. SG also improved short-term and working memory.

*Study 9:* Hsin Chu's study on the impact of group music therapy on depression and cognition in elderly persons with dementia (Chu et. al, 2014). The study utilized a prospective, parallel-group design with permuted-block randomization music. 104 (n=104) older persons with dementia were randomly assigned to either an experimental, receiving 12 sessions of group music therapy (two 30-min sessions per week for 6 weeks), or control group, receiving usual care. Data was collected 4 times- 1 week before treatment, after the 6th session of treatment, after the 12th session of

FIGURE 1: Study Summaries & Conclusions

Study #	Author	Year	Variables/Objectives	Methods	Conclusions
1	Calovini	1993	Anxiety (mental health)	11 subjects observed for 4 months, with 8 receiving therapy; anxiety levels measured before and after sessions using: <ul style="list-style-type: none"> <li>• STAI self-reporting questionnaire</li> <li>• Physiological measures (blood pressure, pulse rate, etc.)</li> </ul>	1 session is not sufficient for improving health.
2	Longfield	1995	Pain, fatigue, anxiety (physical condition/mental health)	8 subjects observed for 5 days after 45-minute sessions; pain and anxiety levels measured before and after sessions using: <ul style="list-style-type: none"> <li>• SFMPQ questionnaire for pain</li> <li>• LASA scale for mood</li> </ul>	Multiple sessions show higher effectiveness.
3	Krout	2001	Pain, physical comfort, relaxation (physical condition)	80 subjects observed for 90 single-session music therapy interventions on a regular schedule; physical condition measured before and after sessions using: <ul style="list-style-type: none"> <li>• Independent observation</li> <li>• Self-reporting</li> </ul>	Long term music therapy is effective.
4	Wlodarczyk	2003	Spiritual/Religious well-being (mental health)	10 subjects observed in 2 sessions (A- music therapy and B- non-music therapy), with half in patterns ABAB and half in BABA; spiritual well-being measured after sessions each session using: <ul style="list-style-type: none"> <li>• SWBS scale</li> </ul>	Repeated music therapy sessions are effective.
5	Hilliard	2003	Quality of life	80 subjects observed with half receiving musical therapy and half receiving routine services; length and quality of life observed using: <ul style="list-style-type: none"> <li>• HQOLI self-reporting questionnaire</li> <li>• Time of death relative to last visit</li> </ul>	Length of life unaffected, but quality of life improved.
6	Takahashi	2006	Improvement of severe diagnosed dementia	Moderate/severe dementia elders observed after weekly group music therapy sessions and compared to subjects in non-music therapy sessions; improvement in dementia measured after the start of therapy using: <ul style="list-style-type: none"> <li>• Systolic blood pressure</li> <li>• Cortisol level</li> <li>• Intelligence assignment</li> </ul>	Music therapy is more effective than non-music therapy for dementia patients.

7	Verghese	2014	Risk of illness onset	469 subjects without dementia observed about 5 years after receiving music therapy treatment; risk of dementia measured using: <ul style="list-style-type: none"> <li>cognitive-activity and physical-activity scales in increment-based units associated with reduced risk</li> </ul>	There is an association between cognitive activity and decreased risk of dementia.
8	Särkämö	2014	Improvement of mild diagnosed dementia	Subjects with mild-moderate dementia observed for 10 weeks in either a singing group, music listening group, or control group; mood and cognitive ability monitored	Music therapy can increase cognition in mild patients.
9	Hsin Chu	2014	Depression, cognition in dementia patients (mental health)	104 subjects with dementia received 12 music therapy sessions or control sessions, and observed; depression and cognitive function measured after 6th and 12th sessions, and before and after treatment	Music therapy improves depression & cognition.
10	Murabayashi	2019	Depression, dementia, social withdrawal (mental/physical health)	115 subjects observed in either musical therapy group or control group for 12 weeks, and then in the other for 12 weeks; cognition, physical function, and psychophysical health measured using: <ul style="list-style-type: none"> <li>VFT Test (cognitive)</li> <li>TUG Test (physical)</li> <li>Geriatric Depression Scale (psychiatric)</li> </ul>	Music therapy improves mental and physical health.

treatment, and 1 month after the final session. Results of the study are listed below:

1. Group therapy reduced depression; improvements occurred immediately after music therapy and were apparent throughout the course of therapy.
2. Cognitive function significantly improved after the 6th session, the 12th session, and 1 month after the sessions ended; short-term recall function improved for dementia patients particularly

*Study 10:* Murabayashi's study on the effects of music therapy in frail elderly patients, age range 65-89 years (Murabayashi et. al, 2019). having one or more care needs regarding social withdrawal, dementia, or depression based on Kihon Checklist (Japanese long-term care insurance system). 115 participants were each

randomly assigned to either a musical therapy-first group, or a waiting-first group for 12 weeks (first period) and then to the other group for 12 weeks (second period). A 4-week washout period was observed to reduce carryover effects. These 45-50 minute sessions consisted of singing familiar songs, instrumental activities, and physical exercise with music. Methods and outcomes of the study are listed below:

1. Cognitive function was measured by the Verbal Fluency Test (VFT); The music therapy-first group showed.
3. Physical function measured by the Timed Up and Go Test (TUG).
4. Psychophysical health measured by the Geriatric Depression Scale 15-item version (GDS-15).
5. Music-therapy periods consistently showed higher levels of improved health across all three categories.

## Discussion

In comparing the data provided by the ten empirical studies, a clear link can be established between musical therapy and health benefits in elderly patients in hospice/palliative care. Music therapy is an effective mechanism in end-of-life treatment and care, but to a certain extent. From each of the ten studies, it can be concluded which type of therapy is the most effective. The summary is as follows:

(Figure 1)

1. Study 1 (Calovini) observing the state of anxiety in hospice care patients showed no statistically significant difference in patient anxiety, blood pressure, pulse rate, finger temperature, etc. before and after a single music therapy session. Thus, it can be concluded that one session alone is limited in its ability to decrease anxiety.

2. Study 2 (Longfield) observing pain and mood in hospice patients showed a statistically significant decrease in pain, and a statistically significant increase in mood. This study was conducted over the course of five days, so it can be concluded that multiple music therapy sessions may decrease pain and improve mental health. Study 3 (Krout) supports the use of long-term therapy; it observes pain control, physical comfort, and relaxation across 90 sessions, showing significant improvements in all three variables. Study 4 (Wlodarczyk) supports this as well, this time showing a significant increase in spiritual well-being after multiple 30-minute music sessions. Lastly, Study 10 (Murabayashi) observing improvements in mental and physical health in an elder group treated with long-term music therapy, further corroborates this conclusion.

3. Study 5 (Hilliard) observing the quality and length of life, as well as time of death in relation to the last visit showed a statistically significant increase in quality and length of life in patients receiving music therapy. However, the data showed no significant difference between the control and experimental groups in terms of

time of death relative to the last visit. Thus, it can be concluded that physical condition can only be improved to a certain extent, given the increase in life length but inconclusive data regarding time of death relative to the last visit.

4. Study 7 (Verghese) observing the prevention of onset of dementia showed a statistically significant decrease in risk of dementia in patients that received music therapy treatment 5 years before. However, though nearly all the subjects eventually developed some type of dementia or related illness, it can only be concluded that musical therapy improves prevention to a small extent. Study 9 (Hsin Chu) and Study 8 (Särkämö), observing the improvement of patients with mild dementia, both show that music therapy increased cognition more than non-music therapy did in similar patients. Study 6 (Takahashi) observed the improvement of dementia in moderate to severe patients, and showed a statistically significant increase in their cognitive functions.

## Conclusion

In summary, music therapy is an efficient therapeutic technique to improve the physical and mental health of elders in hospice and palliative care. Those looking to implement it into the care schedule of any elders can ensure the most efficiency in health improvement by offering therapy sessions on a long-term scale and over time. However, it should be acknowledged that physical health has only been shown to improve in limited amounts, and mental health, stress, and mood improvement should be the main emphasis (Porter et. al, 2017). Additional research is needed to track long term effects of repeated music therapies, specifically those diagnosed with terminal mental and physical illnesses. Drawbacks of these studies include that many measurement tools were not designed specifically for the terminally ill. Further studies are recommended with such tools. Additionally, some studies did not use a large enough sample size to represent the population of elderly, and further

research is needed to establish musical therapy as a legitimate therapeutic practice.

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# Increase in Relative Highway Fatalities During the COVID-19 Pandemic with Respect to Driver Age Distribution

Shani Getz

Belmont High School, United States  
sgetz22@belmontschools.net

## Abstract

The beginning of the COVID-19 pandemic in March, 2020 marked the start of a significant decrease in total vehicle miles traveled. This decrease was caused by lockdowns, increased unemployment and teleworking, and the shutdown of many different institutions. However, there has been a puzzling increase in relative highway fatalities per 100 million Vehicle Miles Traveled (VMT). In this paper I hypothesize that this increase in relative highway fatalities was due to a change in age profile of the drivers that was caused by rising unemployment rates and teleworking. I developed a model to represent the total highway fatalities as a weighted sum of each age group's contribution so that, by varying the age distributions, different total highway fatalities would be calculated. Age distributions were estimated for pre-COVID and during COVID times using various datasets. Despite using two different approaches with the model, the estimated age distributions for pre-COVID and during COVID ended up being too similar to demonstrate a significant increase in highway fatalities, and thus were unable to serve as evidence for the documented increase. However, different methods of estimation or including more factors could better showcase the change in driver age composition and, furthermore, better explain this increase in highway fatalities per 100 million VMT.

## Introduction

On March 13th, 2020 in the United States, in response to the prevalence of the infectious SARS-CoV-2 virus, the initial COVID-19 pandemic lockdown started. A national emergency proclamation from the president began the chain reaction of closures to prevent the spread of the virus (Trump, 2020). Schools, offices, stores, and other establishments shut down, putting "nearly 10 million Americans out of work" in just the first few weeks (Taylor, 2020). General unemployment rates soared with some parts of the population impacted more than others; women, at 14.3%, and young adults, at 25.3%, experienced some of the highest unemployment rates, exceeding their Great Recession rates by 4.9% and 5.3%, respectively (Kochhar, 2020). With this decrease in employment, along with enforced lockdowns, an increase in teleworking, and social distancing mandates, the logical effect would be more people staying home. Online grocery sales surged, sales increased by 79% (Leatherby & Gelles, 2020), suggesting that a significant sector of the population did not even drive to the grocery store to buy food. Based on this data, the assumption can be made that fewer people drove during these initial pandemic months.

The conjecture that the fewer people drove is, indeed, accurate, with a fall of around 50 trillion vehicle miles traveled (VMT) between March 1st and April 1st (Figure 1a). Overall, there was a

13.2% decrease in overall miles traveled in 2020 (NHTSA, 2021). Consequently, I assumed that the number of highway fatalities would decrease as well. However, the total number of highway fatalities continued in the same pattern as before after the pandemic began, and even increased (Figure 1b). To normalize the number of fatalities to the total driven miles, the Bureau of Transportation Statistics divided the two numbers and calculated the number of highway fatalities per 100 million VMT (Figure 1c). There was a sharp increase in relative highway fatalities from just before the pandemic started compared to during the pandemic -- the average until 1/1/2020 was 1.12 fatalities per 100 million VMT and increased to 1.47 after 4/1/2020. This reflected a significant increase of 0.35 highway fatalities per 100 million VMT (31.25% increase), from before to after the start of the pandemic (T-test returned a  $p < 0.001$ ).

The question that these data pose is: what caused this relative increase in highway fatalities? The answer to this question is still unknown. However, some offered speculative reasonings, suggesting that this occurrence can be attributed to higher highway speeds, a heightened sense of general distress and craze from the pandemic, and a shift in the profile of the remaining active drivers (NHTSA, 2021; Liao & Lowry, 2021; Meyer, 2020). Still, uncertainty remains about the cause of this phenomenon. Here, I hypothesize that the majority of the increase in highway fatalities per 100 million VMT was not due to a direct mental effect of COVID-19 or increased speeding, but rather a change in the profile of drivers. Due to lockdowns, unemployment, and teleworking in the early phase of the pandemic, the profile of the drivers on the roads may have changed. In particular, since unemployment and teleworking likely has a differential effect on different age groups, I hypothesize that the age profile of the drivers may have changed and this change could potentially explain, at least in part, the increase in fatalities per 100 million VMT.

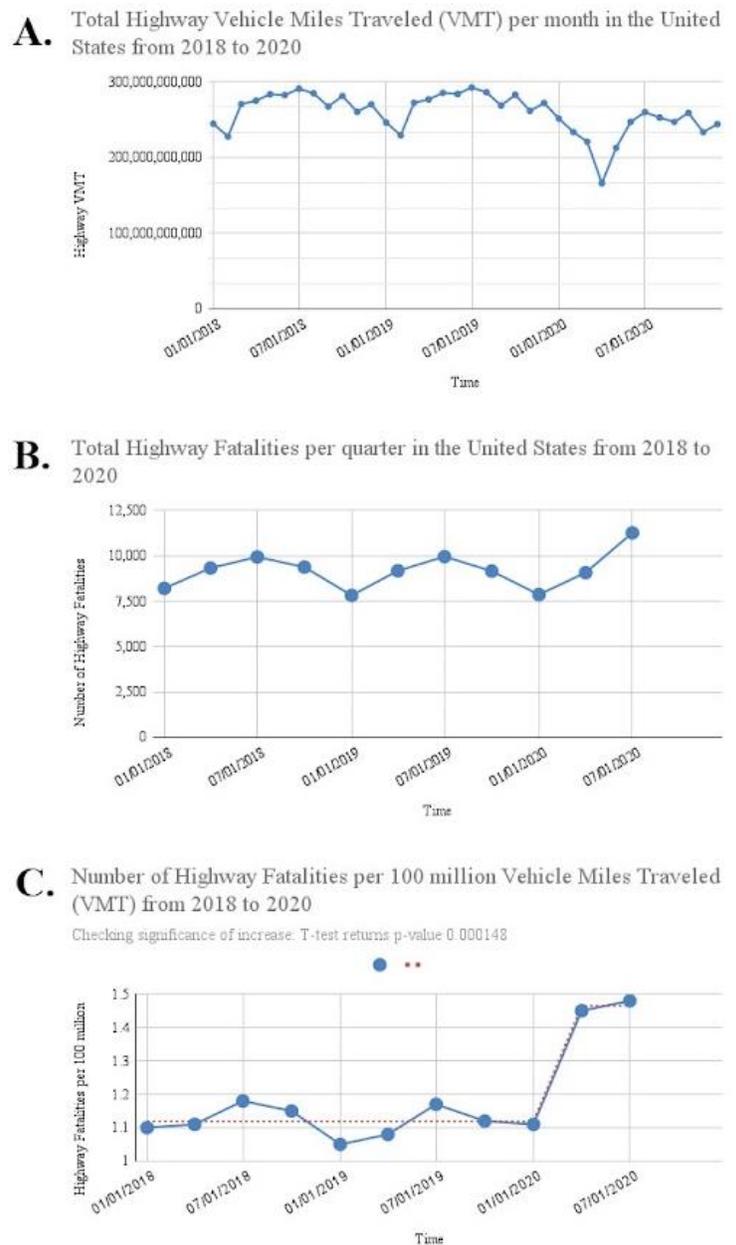


FIGURE 1. (a) Total Highway VMT in the United States from 2018 to 2020 recorded monthly. (b) Total Highway Fatalities in the United States from 2018 to 2020 recorded quarterly. (c) Number of Highway Fatalities per 100 Million VMT recorded quarterly. Data retrieved from the Monthly Transportation Statistics from the Bureau of Transportation Statistics of the U.S. Department of Transportation.

## Methods

Based on an initial inquiry about how the pandemic affected transportation, preliminary research was conducted through the Google Scholar search engine, with keywords such as 'highway fatalities', 'covid-19', '2020' and other versions and permutations of these. Using general Google searches, raw data was found and used from various government bureaus or private associations and organizations like the Bureau of Transportation Statistics, the Bureau of Labor Statistics, the AAA (American Automobile Association), and the Gun Violence Archives. Road rage data from the Gun Violence Archives, accessed on August 15th, listed the latest 2000 instances of gun-related road rage, most of which resulted in either injuries or fatalities, the earliest being on November 9, 2018.

### *Generating Figure 1*

Data from the Bureau of Transportation Statistics was plotted using Google Sheets (Figure 1a and Figure 1b). Figure 1c was created through the same data set, with values of the number of Highway Fatalities per 100 million VMT. Additionally, the average values of before and during the pandemic were plotted in a red dashed line, where the before includes all values from 1/1/2018 until 1/1/2020. A Google Sheets T-test of unequal sized groups was then run to compare the different values from before and during the pandemic, resulting in a  $p < 0.001$ .

### *Model of number of highway fatalities per 100 million VMT based on age groups*

I modeled the number of highway fatalities per 100 million VMT as a weighted sum of each age group's contribution to the fatalities (Equation 1). I denoted the number of highway fatalities per 100 million VMT pre-COVID as  $y^P$  and during COVID as  $y^C$ .  $A$  represents the total number of age groups. The variable  $w_i$  in both the pre-COVID and during COVID equations denotes the fraction of drivers within the  $i$ th age group. The variable  $y_i$  reflects the total number of highway fatalities per 100 million VMT if all drivers were from age group

$i$ . Here we assume that  $y_i$  do not change due to the pandemic, and the only difference between pre-COVID and COVID times is the fraction of drivers in each age group.

$$y^P = \sum_{i=1}^A w_i^P y_i \quad y^C = \sum_{i=1}^A w_i^C y_i$$

Equation 1: The models for the number of highway fatalities per 100 million VMT pre-COVID ( $y^P$ ) and during COVID ( $y^C$ ) using a weighted sum of each age group's contribution to the total number of highway fatalities.

### *Estimating the age-specific Highway fatalities per 100 million VMT*

The values of  $y_i$  values were estimated in two different approaches:

**Approach 1.** In the first approach,  $y_i$  was calculated in 3 parts: a relative road rage index, a fatality crash index, and an unknown factor  $x$  (which was extracted from the data). The relative road rage index indicates a relative value that identifies for each age group the level of recklessness based on data from the AAA, where each age group had a value per aggressive action that represented the percentage of that age group that have participated in that action. The process to obtain the relative road rage index began by identifying which of the road rage actions listed in the table the AAA provided (Tailgate, Yell, Honk, Gesture, Block from changing lanes, Cut off, Confront, and Bump/Ram) would qualify as or could potentially lead to a fatality. After choosing 4 such categories (Block from changing lanes, Cut off, Confront, and Bump/ram) as those that would qualify, I calculated the relative increase in participating in this action in the specific age group. I first calculated the average percent of all age groups. Then, each action's percent value was divided by the average of that action. By averaging the resulting values per age group, the relative road rage indices were obtained.

The fatality crash index was taken from the AAA 2015 study that showed that individuals in the youngest age groups and the oldest age group were more likely to be involved in a fatal crash with rates per age group. Because the age groupings used in the study did not align with those in this study, it was assumed that the rate was constant across all ages within each age group range. The mean was then found for each of my study's age groups and served as the fatality crash index. The two indices were multiplied together to reflect the overall recklessness of drivers in each age group. I assume that the number of Highway fatalities per 100 million VMT is proportional to the combined index and therefore multiplied the indices by an unknown proportion  $x$ , which is later found by fitting to the pre-COVID data.

The  $wiP$ , or what percent of the total number of drivers each age group is, was found with data about distribution of licensed drivers. Once again, the age groupings in the data found were not consistent with those in my study, so the same methods had to be employed as previously stated with the fatality crash index. The given pre-COVID average number of highway fatalities per 100 million VMT, 1.12, was plugged in as  $yP$  and  $x$  was solved for using the values of  $wiP$  and  $y_i$ , returning  $x = 0.68$ .

The fraction of drivers in each age group during COVID,  $wiC$ , was found by taking two factors into account: (i) the increase in unemployment rate from February to May, multiplying the pre-COVID fractions by  $(1 - \text{additional unemployment rate})$ ; and (ii) the fraction of people that are teleworking, multiplying by  $(1 - \text{the percent of employed people teleworking in May})$ . Once the new  $wiC$  values were found, I normalized them again to reflect the fraction of each age group (Figure 3). The  $x$  value and  $y_i$  values were multiplied by the  $wiC$  values (the distributions during COVID) to find the  $yC$ , which resulted with 1.125 highway fatalities per 100 million VMT, reflecting only a small increase from 1.12 (0.45% increase).

**Approach 2.** In the second approach, only the fatality crash index was used as  $y_i$  and an  $x$  value was not necessary. Because this index was already in the correct units, it assumes the  $y_i$  role perfectly; it represents the number of crash fatalities each age group would cause on its own. However, when plugged in with the  $wiP$  distribution values, the  $yP$  did not equal 1.12, but rather 1.56. When the calculated  $wiC$  distribution values were multiplied by the  $y_i$  values, the  $yC$  equaled 1.59, reflecting an increase of 1.92%.

### *Generating Figure 3*

I analyzed the list of gun violence road rage events and subsetted the data to highways by searching for road names that had '-' [dash] in their name and included one or more people killed (using Google Sheet functions). The remaining data was then grouped quarterly (summed values for every 3 months) in order to match the relative highway fatalities that were recorded quarterly. After lining up the data and finding the timepoints that had values for both the highway fatalities per 100 million VMT and the gun violence road rage, a scatter plot was made, with the x-axis being the number of highway fatalities per 100 million VMT and the y-axis being the number of highway fatalities due to gun violence road rage. The line of best fit that data was also plotted. The  $R^2$  value was found and from there, the p-value was calculated to check if this correlation is statistically significant (using an online calculator that used the  $R^2$  and number of data points).

### **Results**

To test if indeed there was a statistically significant difference between the before and during the pandemic subsets of relative highway fatalities, a T-test was run that returned a  $p < 0.001$ . With this p-value, it proved itself to be significant. To try to explain this significant increase in highway fatalities, the change in age profile needed to be assessed. Firstly, the baseline age profiles of the drivers were evaluated to check how each group contributed to the total fatalities before COVID-

19. Due to a lack of access to the most accurate, fitting data, the distribution of age groups within the total number of drivers was taken from data about licensed drivers. I used these percentages to represent the distribution of active drivers pre-COVID by age (blue). The fact that I used licensed drivers rather than active drivers may pose inaccuracies in the distribution.

Next, to calculate the distribution of age groups driving during COVID (red), data on unemployment and teleworking were used to alter the percentages and then re-normalize them so they add up to 100% (Figure 2). According to my estimates, there did not seem to be much variation in the age profile of drivers from pre-COVID to COVID. The two factors had opposite effects, where the product of rise in unemployment and the percent teleworking counteracted each other and ended up keeping the overall fractions similar. However, social distancing measures and driving experience were not taken into account, thus my estimated fractions may be inaccurate. According to a Michigan Medicine study, over double the number of older adults felt lonely or isolated during the early months of the pandemic due to social distancing and COVID-19 restrictions (Gavin, 2020). Additionally, the oldest age group in data from the CDC, people above 60 years of age, consistently had the greatest percentage of participation in mitigating and safe behaviors during the pandemic, like maintaining 6 feet of social distance or avoiding restaurants and other public places (CDC, 2020). Another source mentioned their findings that older individuals were more consistent over time and were more quick to adopt behavioral changes, like the previously mentioned ones (Kabiri et al., 2020). The CDC explains how teens are at a greater risk of car accidents and fatalities due to inexperience, lack of seatbelt use, distracted driving, speeding, and alcohol use (CDC, 2021).

Distribution of Drivers' Ages before and during COVID

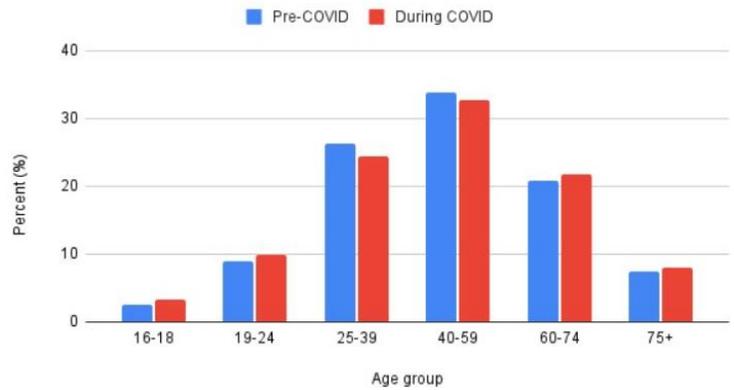


FIGURE 2: Distribution of licensed drivers by age pre-COVID and estimated distribution of drivers per age group during COVID based on unemployment and teleworking data. Data retrieved from the Office of Highway Policy Information from the Federal Highway Administration, AAA Foundation for Traffic Safety, U.S. Bureau of Labor Statistics, and Pew Research Center.

Once the changes in percentages of each age group were noted, I used data on road rage and reckless driving by age group as a proxy for each group's contribution to the overall sum of highway fatalities. Aggressive driving, the term for less extreme road rage, is defined by the AAA as "any unsafe driving behavior, performed deliberately and with ill intention or disregard for safety" ("Aggressive Driving", n.d.). Studies have shown that certain sectors of the demographic exhibit higher levels of road rage and reckless driving while others exhibit lower levels. For example, in a study by the AAA on self-reported aggressive driving behaviors, "drivers ages 25-39 were the most likely to report the majority of the behaviors, including tailgating, yelling, honking, gesturing, cutting off, or exiting their vehicle to confront" (AAA, 2016). Additionally, there has been a gradual increase in road rage and gun violence in the past few years with more substantial jumps in 2020 and 2021, which could provide some evidence for the paralleled increase in relative highway fatalities (Deliso, 2021).

In order to use data on how age groups differ in terms of road rage, I checked for a correlation between the increase in relative highway fatalities per 100 million VMT and highway fatalities due to road rage, during the pandemic (Figure 3). With a  $p = 0.019$ , there is a statistically significant correlation between these two datasets. Therefore, a model can be constructed that uses ratios taken from studies on road rage levels of different age groups.

Correlation between Highway Fatalities per 100 million VMT and Highway fatalities due to road rage since October, 2018

measured quarterly,  $p$  value = 0.019

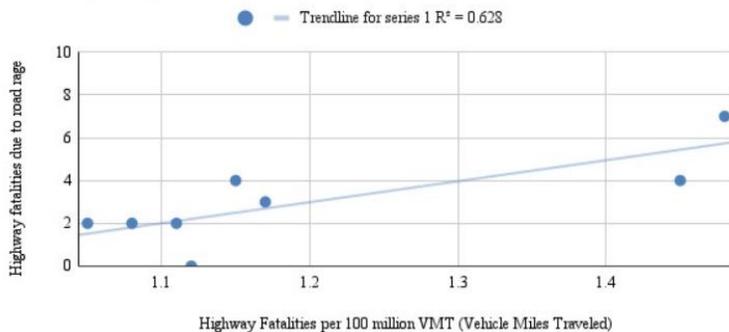


FIGURE 3. A scatterplot of the correlation between the relative number of highway fatalities per 100 million VMT to the filtered highway fatalities due to gun violence road rage. Data retrieved from the Bureau of Transportation Statistics and the Gun Violence Archives.

In this model, each age group has contributed its factor to the overall number of relative highway fatalities. This is done through a weighting process (Methods). Through two different tactics, one using highway road rage deaths data and age group distribution of fatalities in crashes data and the other only using the second dataset, results were obtained. The first method resulted in a 0.45% increase from the pre-COVID average of 1.12 highway fatalities per 100 million VMT to an estimated 1.125 highway fatalities per 100 million VMT during COVID. This does not fully explain the 26.78% recorded increase. The second method resulted in a 1.92% increase from the distribution values before and during COVID, which also does not fully explain the aforementioned recorded

increase, but the average pre-COVID highway fatalities value of 1.12 was not used.

## Discussions

It was surprising that, in my model, the distribution of ages did not change substantially despite calculations done to factor in increasing unemployment rates and teleworking rates. An improved model could more accurately show the change in driver age distribution if there exist additional factors that would do such.

Other changes in the distribution of the driving demographic besides age could have made an impact on the increase in relative highway fatalities, such as a change in the gender distribution, a change in the socioeconomic distribution, and a change in the education level distribution. Another direction that one could take this preliminary research is to develop a similar model with the socioeconomic status distribution or education level distribution as opposed to the age distribution. Studies have shown that, on average, wealthier people had the privilege of staying at home during the pandemic while poorer populations did not always have this option (Valentino-DeVries et al., 2020). This implies that research into the changes in distribution of socioeconomic status of drivers could show more drastic shifts in active drivers from before to after the pandemic began in comparison to the age distribution. Thus, it might account for more of the increase in relative highway fatalities. Such findings could be taken in their own context or merged with the findings in this paper to compare which change in distribution has the greatest correlation with the increase in relative highway fatalities during the COVID-19 era.

As stated earlier, there are several other factors that were not accounted for in my calculations, like driving inexperience, increased speeding, likelihood to stay at home during the COVID-19 pandemic, and more. Beyond this, my model could have possibly shown more of an increase in highway fatalities if there was more precise and accurate data available on the age distribution of active drivers rather than licensed drivers. For

example, further investigation into the population's tendency to leave the house during the pandemic by age could better address the greater health risk factor for the elderly and the implications of that on the active driver distribution. Another option for a future direction is to actively collect data on the age and miles driven on the highway during the pandemic using surveys, but there are limitations to data that can be collected and it may not be relevant, as the situation has changed since the onset of the pandemic in March and April of 2020.

Overall, despite not being shown as significantly responsible for the puzzling increase in highway fatalities per 100 million VMT in the U.S. with my model, the age distribution and road rage tendencies of drivers are very important factors that impact the safety of our country's people during this pandemic. This analysis provokes further questions and investigations into the change of driver distribution due to COVID-19.

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# Association Between BMI and COVID-19 Clinical Outcome Severity: A Systematic Review Comparing Data from Asian and Western Countries

Tanisa Goyal

King George V School, Hong Kong  
goyalt1@kgv.hk

## Abstract

Given the global significance of COVID-19, it is crucial to discuss potential factors that correlate with the severity of clinical outcomes for patients. This study examines the association between obesity, characterized by high BMI, and increased severity of adverse clinical outcomes for COVID-19 patients, quantified through ICU admission numbers. A total of 20 studies between 2020 and 2021 from both Western countries and Asian countries were systematically reviewed, and data regarding the nature of the study, number of patients in various BMI groups, and ICU admissions were extracted. The studies were found in a medical research database (PubMed) and qualitatively screened to determine their relevance. The correlation between obesity and ICU admissions was then calculated, ensuring that two distinct correlation values were determined: one for the Western-centric studies and one for the Asian-centric studies. The former showed a stronger positive correlation. Given that obesity may serve as an indicator for severe clinical outcomes, this research can be used in relevant geographical locations for the betterment and increased caution of patient care.

*Keywords: COVID-19, Body Mass Index (BMI), Obesity, Clinical Outcome Severity, Intensive Care Unit (ICU)*

## Introduction

In January of 2020, the World Health Organization established an outbreak of “a novel coronavirus” (World Health Organization, n.d.). Over the span of almost two years, the source of the infection, SARS-CoV-2, has caused over 216 million cases, and over 4 million deaths (Google News, n.d.).

Given the broad range of manners by which this infection can manifest in different patients, it is crucial to establish the influence of various prognostic factors that contribute to the potential severity of their clinical outcomes (Földi et al., 2020). This will therefore allow both physicians and patients to gain an invaluable insight into developing improved and potentially earlier treatment of the disease. Several diseases have been previously recognized as factors correlating with adverse clinical outcomes in COVID-19 patients, such as diabetes and cardiovascular diseases. Given that such diseases often have relations with excess body fat, obesity may be another risk factor predisposing adverse clinical outcomes. Several sources have already concluded that obesity can be strongly associated with the severity of COVID-19, for reasons that will be discussed later in this review (Klang et al., 2020) (Giacomelli et al., 2020).

Despite this, there is a lack of literature investigating the direct relationship between obesity and ICU admissions rates, to demonstrate the severity of the patient's condition given this specific biological characteristic. This is especially

true in the case of comparing said relationship for patients across different geographical locations, despite the fact that ethnic variations in BMI classes exist. (The World Obesity Federation, n.d.) As such, this systematic review will compare the association between obesity and ICU admissions rates in studies focused on Asian subjects and Western subjects.

## Methodology

### *Search Strategy*

A systematic search was performed through a scientific database, namely PubMed, in search for studies between the years 2020 and 2021, as this is the ongoing period of the COVID-19's impact globally. Specific search terms were used with a filter to ensure all results were of open-access journal articles. The following search key was used: ((covid 19) OR (coronavirus) OR (SARS-cov-2)) AND (BMI), thereby combining various iterations of COVID-19, whilst leaving a broader scope for BMI related results.

### *Selection and Eligibility Criteria*

After using a reference manager (Zotero) to remove duplicates of the journal articles found, the titles and abstracts of the remaining articles were screened following a rigid selection and eligibility criteria. The following inclusion criteria were used:

1. Journal articles written in English
2. Journal articles reporting BMI classes of hospitalized patients with confirmed SARS-cov-2 infections
3. Journals reporting each BMI class's respective ICU admit rate as an indicator of the severity of the patient's condition
4. Patients were all adults above the age of 18
5. Prospective or retrospective cohort studies
6. BMI classes adhered to the following distinctions, as established by the World Obesity Federation (n.d.):

- a. Asian countries/patients: BMI  $\geq$  24.0 = Obese
- b. Western countries/patients: BMI  $\geq$  30.0 = Obese

The following exclusion criteria were used:

1. Review articles, letters and commentaries were to be rejected
2. Duplicate studies were to be rejected
3. Studies involving patients that have conditions significantly impacting their BMI were rejected (e.g. studies focused on pregnant women, pediatric patients, etc.)

### *Data Extraction*

Data extracted from the remaining eligible studies were organized on a spreadsheet using Microsoft Excel. The following data were extracted from each included study:

1. Author(s)
2. Title
3. Publication Date
4. Digital Object Identifier (DOI)
5. Study Design
6. Study Location
7. Study Population
8. Population Age Range
9. Total Number of Intensive Care Unit (ICU) Admissions/Critical Condition Patients
10. Total number of patients in the non-Obese category
11. Total number of ICU/Critical Condition Patients in the non-Obese category
12. Total number of patients in the Obese category
13. Total number of ICU/Critical Condition Patients in the Obese category

### *BMI Category Classification*

As mentioned previously, BMI categories were defined using pre-established guidelines by the World Obesity Federation (n.d.). The obesity category's values for Western and Asian patients were BMI  $\geq$  30.0 and BMI  $\geq$  24.0 respectively.

## Results

### PRISMA Flow Diagram

Figure 1 below shows a diagram of the study selection process in detail. A total of 736 sources were found from the initial search, of which 604 were excluded after assessing whether their titles and abstracts demonstrated any relevance to the focus of this research. Then, the remaining 132 articles were evaluated, adhering to the aforementioned selection and exclusion criteria. A total of 20 studies were finally selected and included for this systematic review. 17 of them were found to be Western-centric, and 3, Asian.

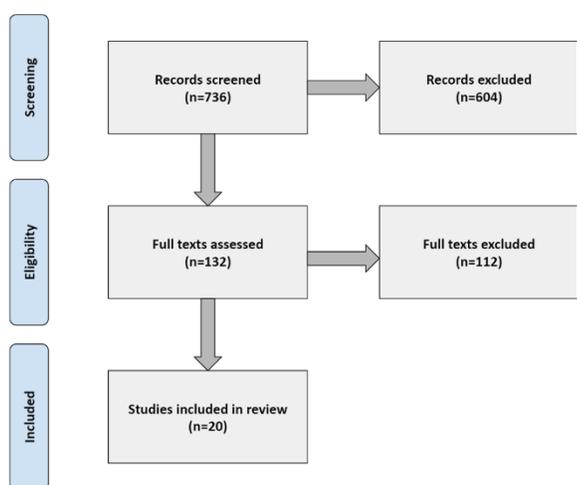


FIGURE 1: PRISMA Flow Diagram showing the screening process for eligible studies used in the research

### Raw Data

After gathering the raw data needed to conduct this systematic review, basic statistical analysis was carried out using the information retrieved.

This data generally establishes that there are a greater proportion of patients with BMIs resulting in obesity that were admitted to the ICU, or considered patients of critical condition. Majority of these studies were conducted in the United States (n=8), with other European countries including Italy and France. The two

Asian regions that were included were China and South Korea.

### Statistical analysis

In the first section of this statistical analysis, it is crucial to establish whether a higher proportion of the obese patients in each study's population were admitted to the ICU compared to non-obese patients. To do this, the number of obese ICU patients were found as a fraction of the total number of obese patients, and compared to the proportion of non-obese patients in the ICU.

Out of the 20 studies included, the vast majority of them showed a greater proportion of obese patients in the ICU compared to non-obese patients (n=16). There were two studies in which there was a greater proportion of non-obese patients in the ICU than obese patients, however, the difference between the two were not substantial. Two studies showed included only ICU patients within their cohort populations, and therefore were not included in this comparison. In order to determine the association between obesity and ICU admissions rates, the number of obese ICU patients as a percentage of the total number of obese patients was graphed against the ICU admission numbers as a percentage of each study's population. These were placed on a scatter plot, and the correlation between the two were found, for both Asia-based studies and Western-based studies. The scatter plots can be seen in Figures 2 and 3 below.

When calculating the correlation values for each scatter plot, the following equation was used:

$$r = \frac{\sum(x - \bar{x})(y - \bar{y})}{\sqrt{\sum(x - \bar{x})^2(y - \bar{y})^2}}$$

where  $r$  = correlation coefficient

$$x = \frac{\text{number of obese ICU patients}}{\text{total number of obese patients}} \text{ values in the sample}$$

$$\bar{x} = \text{mean of the } \frac{\text{number of obese ICU patients}}{\text{total number of obese patients}} \text{ values in the sample}$$

$$y = \frac{\text{total ICU admissions}}{\text{total population of study}} \text{ values in the sample}$$

$$\bar{y} = \text{mean of the } \frac{\text{total ICU admissions}}{\text{total population of study}} \text{ values in the sample}$$

The following results were obtained:

Figure 2	Figure 3
$r=0.9907$	$r=0.5980$

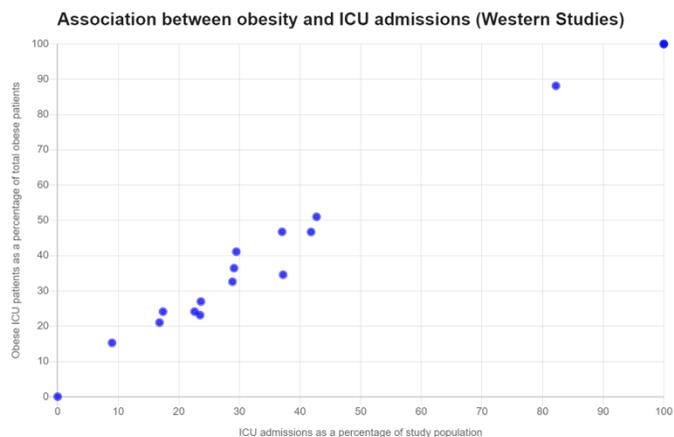


FIGURE 2: Association between obesity and ICU admissions (Western Studies)

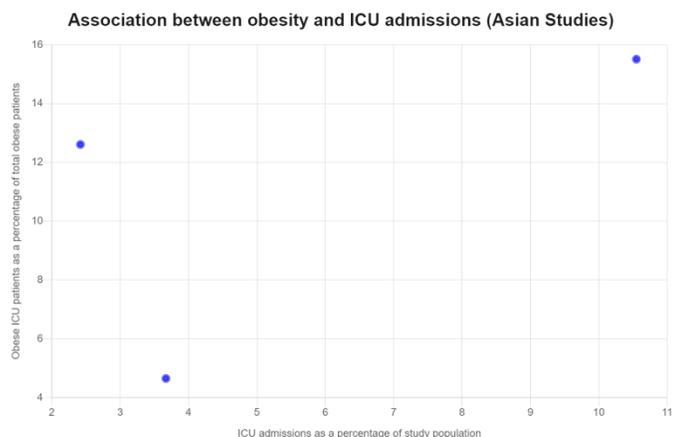


FIGURE 3: Association between obesity and ICU admissions (Asian Studies)

It can be seen that there was a much stronger positive correlation between the two variables for the Western-centric studies, with the difference being 0.3927. The strong positive correlation between the two variables for the Western centric studies is consistent with previous research establishing the increased incidence of adverse clinical outcomes given that a patient is obese (Pranata et al., 2021). Regarding the correlation figure for the three Asian-centric studies, given that there were an extremely limited number of studies centered around Asian patients, the correlation for Figure 3

most likely is not representative of the true relationship between the two variables. The figure, however, still demonstrates a positive correlation between the two variables.

## Discussion

### *Obesity and ICU Admission*

Several studies have explored the relationship between obesity and increased severity of adverse clinical outcomes in general, including increased probability of ICU admission. One highlighted that COVID-19 patients, common comorbidities include hypertension, diabetes, and cardiovascular issues in general, all of which relate to obesity, specifically through pathways in the renin-angiotensin system (a hormone system that regulates blood pressure and fluid balance in the body) (Földi et al., 2020) (TeachMe Physiology, 2021). The same study also showed that patients with higher BMI required more frequent invasive mechanical ventilation (IMV) due to reduced pulmonary reserves and alterations of the chest-wall anatomy, contributing to their need for ICU admission. Obesity is also said to hinder the effectiveness of protective immune functions.

### *Strengths of the systematic review and implications of the research*

This systematic review adhered to a rigorous methodology, screening a large number of journal articles before critically determining those relevant to the research question. Studies from a large range of geographical locations were acquired, and the relationship found has been corroborated with several other studies, including previously conducted meta-analyses on obesity and COVID-19. Being a study that compares the association between these two variables for patients of different geographical backgrounds has crucial implications. This is considering that firstly, there are differences in BMI categories for each geographical group, and secondly, there are varying practices in place from country to country regarding patient care and disease management. Determining distinct associations between the

variables for different geographical backgrounds would therefore provide medical experts in relevant countries with a foundational knowledge for the need for special monitoring of COVID-19 patients with obesity.

#### *Limitations of the research*

A key limitation of this research is the limited range of Asian-centric studies included; given that only three were found to be relevant, this significantly impacted the accuracy and representative nature of the relationship found between obesity and adverse clinical outcomes. Secondly, the statistical analysis conducted was highly simplistic and primarily utilized a simple bivariate scatter plot, which may not serve as detailed, encompassing evidence for the relationship between the two variables. The research also did not consider the influence of other factors and their implications on the severity of clinical outcomes. Finally, when gathering data on the number of patients with varying BMI, the values extracted were limited to large groups, defined by “Obese” and “Non-Obese”, which do not account for further sub-categories that may have had their own significant association with clinical outcome severity.

#### *Potential Future Research*

Whilst one of the criteria used to screen the chosen articles was that the age group was to be adults above the age of 18, most of these studies constituted patients the middle age, which calls into question the relationship between age, BMI and outcome severity. Few studies have discussed this, thereby serving as scope for further research. Additionally, conducting a multivariate statistical analysis would be quite beneficial. This would also allow for the consideration of other factors and their influences, such as more specific chronic diseases like diabetes, that are closely interrelated with obesity. Further investigation into the association between these variables across a more specific range of geographical locations would also be beneficial, as opposed to limiting the research to a distinction

between Western and Asian countries. Given that vaccination programs are currently being implemented across various countries, it would be interesting to understand whether there is a relationship between these variables and the effectiveness of the COVID-19 vaccine.

#### **Conclusion**

In conclusion, the systematic review and basic statistical analysis conducted reinforced that there is a relationship between obesity and the incidence of adverse clinical outcomes. Given that the pandemic is still ongoing, physicians and healthcare professionals should utilize this, and other research, to more closely monitor and treat patients with higher BMI's earlier, thereby reducing the risk of complications.

#### **Conflicts of interest**

The author has no conflict of interest to declare.

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# The Varying Misconceptions and True Effects of Videogames on Psychological Functioning

Gregory Guyumdzhyan  
Belmont High School, United States  
gguyumdzhyan22@gmail.com

## Abstract

This paper explores a variety of published articles and prior research that aim to defog the association between video games and psychological function, and whether they hinder or aid this key function. There are a variety of articles that debate this topic, with some arguing that videogames can lead to mental disorders and mishaps, and others that argue that they are beneficial to the human mind, with some arguing that these can serve as a medical treatment for some. A fundamental that many of these articles lacked was data or research to back them up, and most of those that did display the usefulness and of the use of videogames in psychological function. Through research and studies from Oxford University, Stetson University, and the Victoria University of Wellington, it becomes clear that in controlled quantities videogames of all types can serve as forms of comfort and therapy, aiding the psychological function of the brain and overall wellbeing for many.

*Keywords: Internet-Gaming-Disorder (IGD), Psychological Well-Being, COVID-19, Videogames, Anxiety*

## Introduction

### *The Popularization of Videogames*

Ever since the debut of the Nintendo N64 as the first mainstream console, videogames have grown from a fun pastime to a commonplace item in most homes. Moreover, with mobile devices becoming more powerful and videogame streaming service more and more available, more

people can enjoy videogames without the need for a dedicated console or powerful PC. Videogame streaming services, also known as cloud gaming, works by having the user stream a game live from a company's facility. Currently, the two biggest cloud gaming services are Google Stadia and Nvidia GeForce, and although their biggest drawback is latency, with Microsoft working on its own streaming service xCloud as well, the future is being paved for all to have access to the same games, regardless of what platform is being used. (Gnanasivam, 2021)

*The Argument Against Videogame Consumption*  
Along with the increase in popularity and accessibility, videogames have also become a hot topic for arguments amongst many in trying to understand the effects of videogames on the psychological functioning of the adolescent brain. Parents are worried that their child will grow up socially inept and develop an addiction to videogames, to which they aren't completely without reason. In May of 2019, the World Health Organization formally recognized extensive gaming as a disorder that stems from an addiction to videogames. (Ganser, 2019) Also known as Internet Gaming Disorder (IGD), this obsessive addiction to videogames is in many ways like addictions in correspondence to other substance-related addictive disorders. People who play videogames extensively are prone to withdrawal symptoms, a lack of interest in previously enjoyed activities, and a decline in sociability. (Internet Gaming, n.d.) Although it is true that extensive gaming leads to addiction, there was a lack of

awareness about any potential psychological benefits to gaming in moderation.

### *The Surge in Videogame Consumption*

With COVID-19 and its corresponding lockdowns keeping many quarantined and at home, the prominence of videogames drastically increased. As of March 2020, America saw an increase in time spent playing videogames during the coronavirus pandemic by 45%. (Statista, 2021) Furthermore, as seen by a study from the Entertainment Software Association (ESA), the number of Americans who play videogames leaped from 164 million in 2019 up to 214 million in 2020 then up to 227 million in 2021. (Snider, 2021) Due to the pandemic, the number of Americans playing videogames increased by 50 million in its first year alone, and collectively throughout the pandemic videogame use increased by 67 million. As mentioned prior, people are no longer bound to consoles and PCs for videogame playing. From 2019-2020, mobile gaming recorded a 12% increase in players, and grossed 77.2 billion US dollars in 2020 alone. (Mobile Gaming Industry Statistics and Trends for 2021, n.d.) As demonstrated by the aforementioned data, the pandemic introduced many new gamers to the videogame industry, notably, many casual gamers who had never avidly played in the past.

### *The Cure to Psychological Stresses*

Why though? The pandemic enabled the success of videogames for a few key reasons. Firstly, as mentioned prior, people are home far more and have far less to do. To pass the time, many people are turning to videogames for entertainment. Secondly, humans are social creatures, and videogames enable us to be social in an isolated world. Between March and April of 2020, Microsoft reported a 130% increase in multiplayer engagement on its services. (Smith, 2020) All multiplayer videogames involve interaction and communication between people, and whether they be friends or strangers, multiplayer videogames allowed for humans to remain social.

Most prominently, COVID-19 has brought additional anxiety, stresses, and pain to many young adults. Roughly 1 in 3 teenage girls and 1 in 5 teenage boys have experienced new or worsening anxiety during the pandemic. (Teen Depression During COVID-19 Pandemic: What to Look For, 2021) Videogames can serve as an answer to these stresses plaguing many young adults. Videogames allow players to play in another reality, one where their stresses and troubles in life are nonexistent, hence allowing for them to be happier, improving their psychological wellbeing. (Deleuze, Maurage, Schimmenti, Nuyens, Melzer, Billieux, 2019) A great example of a videogame serving as a comforter is *Animal Crossing: New Horizons*, in which it's success soared as it offered just what the pandemic robbed of people: an escape whilst remaining multiplayer to play with friends. (Zhu, 2021)

### **Method**

To find the proper sources, a select set of search terms were used (ie: Videogames and Mental Wellbeing, Videogames and COVID-19, Internet Gaming Disorder). Using Google Scholar as a basis of web search (large magazines, academic journals, and acclaimed independent databases were considered as well), a plethora potentially useful sources relating videogames and mental wellbeing were found. Of these sources, (n=56) sources directly discussed videogames and its adverse effects on mental wellbeing. Per source, a systematic literature review was performed. This multistep process entailed checking for an author or other form of legitimacy, relevant date to where the source was needed in the research and reviewing the site to which an article is published so that it is academically reliable. For large databases however this process was lightened up, because they have other forms of verifying what was written. For example, although the source from the American Psychiatric Association failed to have an author, what was written was reviewed by a named physician who is aware of the material, along with a date of review. With the

systematic review performed for eligible sources (excluding databases and other reviewed sources), (n=23) viable sources remained that could be used for the INTRODUCTION and RESULTS section. With the viable sources, they were used throughout INTRODUCTION section where needed.

For the results in the RESULTS section, all data/ideas were pulled directly from published research papers and case studies. With the relevancy and quality of data/ideas investigated thoroughly, (n=14) research papers were considered for the results. Although the data/ideas from all the (n=14) research papers were accurate, they were mostly basic and lacked nuance. Out of the remaining considered research papers, (n=3) research papers from Oxford University, Stetson University, and the Victoria University of Wellington provided data and insight that is not only interesting in itself, but when looked at cumulatively reveal that the use of videogames in moderation, regardless of genre, can serve as effective tools in aiding the psychological wellbeing of not only young adults, but the general population.

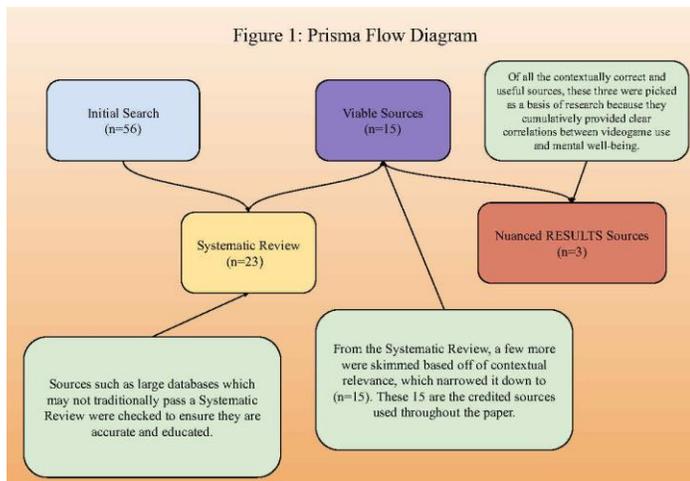


FIGURE 1: Prisma Flow Diagram depicting the METHODS process of diluting sources and narrowing viable sources

## Results

### *Video Gameplay is Positively Correlated with Well-Being*

In the research paper written by Niklas Johannes, Matti Vuorre and Andrew K. Przybylski of Oxford University, they observed player's wellbeing in context with 2 very different games. (Johannes, Vuorre, Przybylski, 2021) One of the games was Plants vs. Zombies: Battle for Neighborville, an action game, and the other was Animal Crossing: New Horizons, a more laid-back life simulation with an emphasis on casual and relaxed. To measure the wellbeing of the players, they initially used forms to gauge the players' current wellbeing, motives to play, and other critical information to the study. Then, they let the players play the games to their leisure for two weeks, with a form that was to be filled out after the two weeks, with a 1-week window to fill out the form. To measure the wellbeing of players, the Scale of Positive and Negative Experiences was used. (Diener, n.d.) This scale accounts for the positive and negative emotions of Player Well-Being, Extrinsic Motivation, Intrinsic Motivation, Player Autonomy, Player Competence, and Player Relatedness. For each positive/negative of each emotion, there was a scale from 1 to 7 that sought to reflect the level of that emotion that the player felt within the past 2 weeks of playing the game. Using histograms, the data from both games were accounted for on the same figure. Although difficult to quantify, the charts represented that those who played more (even those who estimated that they played more) experienced greater well-being than those who were less immersed in their game. The data also reflected that there was almost no difference in wellbeing experienced between the two games, despite being completely different genres.

### *Aggressive Video Games Are Not a Risk Factor for Mental Health Problems in Youth*

In this case study led by Christopher J. Ferguson and C.K. John Wang, these professors of Stetson University displayed the correlation (or lack of) between violent videogame use and long

term mental health symptoms. (Ferguson, Wang, 2021) To be specific, they investigated the stigma that violent games lead to violent behaviors in children, and they wanted to see whether it was true or not. To measure this, they used a sample of 3034 youth from Singapore, with a beginning mean age of 11.26 years of age at T1. Using the ESRB game rating scale, they picked out violent/action-packed videogames and had those participating in the case study play them frequently throughout the case study. They measured their health symptoms every year, with each following year being T2 and T3. By the end of the trial, T3, the mean age was 13.12. At the two intervals (T2 and T3), the participants were asked a variety of questions gauging Somatic Complaints, Depression, Anxiety, ADHD, Social Phobia, and Impulse Control Problems. Their research concluded that the games made no impact on any of these listed aspects of the participants' psychological wellbeing.

#### *The Effects of Casual Videogames on Anxiety, Depression, Stress, and Low Mood*

Throughout this case study, Russel Pine, from the Victoria University of Wellington, along with 3 others, Theresa Fleming, Simon McCallum, and Kylie Sutcliffe explore the effects that the playing of videogames has on combatting Anxiety, Depression, Stress, and an overall negative mood. (Pine, Fleming, McCallum, Sutcliffe, 2020) Focusing more on casual videogames, they found that many articles reported positive effects on anxiety in gamers, giving them less anxiety that lasted upwards of 30 minutes after gameplay. Their research also revealed that videogames that had bright colors, immediate feedback, and clear tasks were especially well with eliminating feelings of anxiety, as well as allowing players to remain calm in an anxiety-provoking situation. Participants demonstrated decreased left frontal alpha brain waves, which demonstrated improvements in mood with the decrease in brain activity which is affiliated with anxiety.

## Discussion

### *The Whole Picture*

Videogames have made themselves more and more prominent in our world today, and with 40% of the world playing them, it becomes crucial to know about the psychological effects of videogames on humans. (Sanjay, 2020) As listed, each study (from RESULTS section) relates videogames and psychology, but each of these studies overlap and blend together to form a comprehensive explanation for how the three relate. In the study that measured how players psychologically reacted to playing casual videogames, there was research on how brain activity changed in response to playing videogames, and it demonstrated specifically how left frontal alpha brain waves decreased in activity when and shortly after the participants played videogames. These waves are indicative of anxiety levels and seeing how they decreased in activity demonstrates that videogames are indeed effective at curbing anxiety levels in people; however, this is in itself incomplete. The study targeted only casual videogames, but by compiling data from another study that covered more games, the results become more viable. Another study of research was the one that pinned videogame usage of both casual and action games. In this study, players play the casual Animal Crossing: New Horizons and the more chaotic Plants vs. Zombies: Battle for Neighborville, from which the researchers surveyed the players before and after playing for two weeks. They surveyed the moods and wellbeing of the players through these surveys and based their findings on the Scale of Positive and Negative Experiences. This scale covers 6 different emotions and both the positives and negatives of the emotions (see RESULTS section for further explanation). Through this scale, they were able to measure any changes in psychological well-being from playing these games, as well as how the changes varied from the casual and aggressive videogame. They found that those who played more of either videogame experienced a better state of well-

being than those that played less. Additionally, the data demonstrated that even the thought of playing more was enough to mimic the psychological effects of actually playing for longer, suggesting that the level of immersion a player experiences with a game affects just how great of a psychological impact that game has on one's wellbeing. The type of videogame didn't matter either because results were similar in all categories of the Scale of Positive and Negative Experiences (only notable difference between the two games was in player relatedness, which scored higher with those who played the more casual game). The data from their research suggested that there is no difference in the psychological well-being from casual and action videogames but, studying any potential negative effects of extremely action packed and violent videogames on youth allows for the conclusion to be more complete. The last study used as a final basis of argument was a case study performed in Singapore, in which roughly 3000 kids with the mean age of 11.26 years of age were exposed to violent videogames. From there, they were monitored for two years annually to measure any change in behavior, measuring a variety of the associated behaviors of violent videogames. Throughout the study, researchers noted no significant changes to the behaviors of the surveyed, which counters the many prior stigmas that tied violent videogames to depression, anger issues, anxiety, and many other negative behaviors.

### *Final Conclusion*

Seeing how each of these studies tied together different aspects of videogames and mental health allows for the following to be concluded; Videogames, regardless of genre, can serve as effective tools in combatting anxiety and improve the overall psychological wellbeing of not only youth, but to the general population as well. Further research into the topic is highly recommended due to unavoidable deficiencies. Deficiencies;

Throughout this research paper, were two significant deficiencies that were bound to come up. First and foremost, there was a lack of quantifiable data available. There was data used throughout the paper where possible to provide the proper context and other benefits, but to the core argument, there was a lack of it. There is no set unit of measurement that is effective in quantifying psychological wellbeing, so researchers have to get creative in gauging this pivotal statistic. The most effective way of doing so is through forms and interviews, and then creating data from there. All the data is based on the moods of the people and their opinions, which makes the data yielded from research (such as the data from the Scale of Positive and Negative Experiences) difficult to trust. These are still useful in coming to a conclusion, but since the data is from questioning, there is a higher likelihood for error. Secondly, there is a lack of research and long-term testing of Internet Gaming Disorder (IGD). Although the rise of videogaming during the pandemic has brought IGD under the spotlight, there is a lack of long-term testing and studies on the disorder due to the fact that it is a relatively new disorder. There are a plethora of research and articles about IGD, but in the current use-case scenario of this research paper, they proved only useful in understanding the disorder, but no more. Having the ability to use data or any sort of figures that breakdown the long-term effects of IGD and levels of well-being in players would allow for a more complete conclusion and strengthen the credibility of the paper.

### *Future Avenues of Research*

A much-needed avenue of research that this research paper opens up is for the future study Internet Gaming Disorder (IGD). To be specific, since this paper establishes that the initial effects of playing videogames are positive, it would be interesting to see what happens for people who play a lot of videogames over an extended period. An interesting topic would be researching the use of videogames amongst a pool of children that vary in prior videogame experience levels, and

checking up on their mental well-being up until adulthood. This would not only measure the likelihood of contracting IGD over an extended period of exposure, but it would also gauge how people mature over time with the common playing of videogames. Another interesting study would be on those who have already officially contracted IGD and how they got it. By studying more about their various experiences with the condition and what their environments/life situations were like when they noticed the disorder plaguing their lives, researchers can be one step closer to discovering a common trigger for the disorder, and then go onto creating preventative methods to counter IGD.

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# Expression analysis of glucan synthase in edible mushrooms *Lentinula edodes* and *Pleurotus eryngii* and their potential for wound-healing applications

Momo Hayashi

Global Indian International School, Japan  
suimu0601momo@gmail.com

## Abstract

Mushrooms are valued in traditional medicine for their healing properties. In particular,  $\beta$ -glucans found in edible fungi, grains, and yeast have been demonstrated to promote wound healing. In this study, we aim to characterize the expression of glucan synthase in *Lentinula edodes* (shiitake) and *Pleurotus eryngii* (eryngii), as well as the expression in organic and conventionally-raised shiitake. Through semi-quantitative RT-PCR, we found that organic shiitake showed the highest expression of glucan synthase, followed by conventionally-raised eryngii and shiitake. Our preliminary findings suggest that organic shiitake has the highest potential for wound healing applications.

*Keywords:* *Lentinula edodes*, *Pleurotus eryngii*, mushroom, wound healing

## Introduction

Mushrooms, known for their umami (うま味), are an integral part of culture and cuisine. Some mushrooms have been used as an herbal medicine for decades. It has, for example, been used for a long time in China and Japan to strengthen the immune system. While most people are aware that mushrooms are valuable food for their low calories, carbohydrates, salt, and fat, many people are still unaware of the important role that mushrooms can play.

Mushrooms are important in traditional medicines although their concept of action is not fully understood. Many studies showed that various edible mushrooms have been reported to generate immunomodulatory and antineoplastic properties (Finimundy et al. 2014, Božena et al. 2017, Fang et al. 2012, Ding et al. 2016). Studies have shown that certain chemicals in edible fungi have beneficial effects on cell activity and on the secondary production of chemical compounds that can strengthen the human immune system and promote the treatment of several diseases (Borchers et al. 2004).

In particular, shiitake and eryngii are found to have beneficial effects purported in other species. *Lentinula edodes*, commonly called shiitake (椎茸, シイタケ), is one of the most studied edible mushrooms. Studies have demonstrated the antitumor, antifungal, antibacterial, anti-inflammatory effects of substances in *L. edodes* (Božena et al. 2017). On the other hand, *Pleurotus eryngii*, also known as king oyster mushroom, is one of the less-studied edible mushrooms. Studies conducted suggest that eryngii may contain substances that activate the immune system (Alam et al. 2011). Furthermore, studies show that extracts from *Pleurotus eryngii* have an effect on anticancer activity, immunostimulating activity, and antiviral activity (Fu et al. 2016). It also contains various compounds that have benefits in the treatment of different

diseases. Both shiitake and eryngii give a variety of health benefits, though their molecular mechanisms are yet to be fully elucidated.

$\beta$ -glucans are carbohydrate polymers present in the cell walls of several species, such as microbes, fungi, yeasts, and certain cereals such as barley and oat (Jurikova et al. 2009). They are among the most prevalent polysaccharides that activate the human immune system, protect against pathogenic bacteria, adverse effects of environmental chemicals, and carcinogens that have impaired immune systems. They also guard against infectious diseases and tumors and help people recover from chemotherapy and radiotherapy (Valverde et al. 2015).

Along with the antitumor, antifungal, and antibacterial effects,  $\beta$ -glucan possesses wound-healing effects (Majtan et al. 2018). In the course of wound healing, the human body undergoes complex processes such as haemostasis, inflammation, proliferation, and remodeling. Inflammation provides resistance to microbial infection; it happens nearly simultaneously with haemostasis. Failed management of any specific mechanism results in pathologically impaired wound healing, such as chronic wounds marked by protracted or excessive inflammatory phases, recurring infections, and delayed wound contraction (Yasuda et al. 2018).

Properties of  $\beta$ -glucan may be effectively used to accelerate the wound healing process. Specifically,  $\beta$ -glucan triggers immune and non-immune pathways, which in turn promote collagen deposition and re-epithelialization (Majtan et al. 2018).

Additionally,  $\beta$ -glucan has been shown to have wound-healing properties in vitro.  $\beta$ -glucan with varying physical and chemical characters are found to be potent inducers of wound closure, greatly influencing the migration and proliferation of cells involved in wound healing through many studies (Majtan et al. 2018). It has been used in the production of bioartificial skin due to its ability

to bind to gelatin and collagen. It is known that  $\beta$ -glucan wound dressing enhances wound healing and decreases pain (Seo et al. 2019).

Here, we aim to characterize the expression of glucan synthase in *Lentinula edodes* (shiitake) and *Pleurotus eryngii* (eryngii), as well as the expression in organic and conventionally-raised shiitake.

## Methods

### Primer design

We found the sequences of the housekeeping gene (18S) of *Lentinula edodes* and *Pleurotus eryngii* from (Yoo et al. 2019) and GenBank FJ572254.1, respectively. The sequence of  $\beta$ -1,3 glucan synthase in shiitake was obtained using transcript ID: 8225 from reference genome W1-26 and transcript ID: 1439750 from *P. eryngii* ATCC 90797 for eryngii. In addition to the 18S primers from (Yoo et al. 2019), the primers were designed using Primer3 with an annealing temperature of 58C and 175-225 base pair amplicon as conditions.

TABLE 1: List of primers used

Primers	Sequence	Amplicon size(bp)
<b>18S (housekeeping gene):</b>		
Shiitake18s_1F Shiitake18s_1R	gcgctacactgacagagcca gcggtgtgtacaaagggcag	178
Shiitake18s_2F Shiitake18s_2R	agggctctttcgggtcttat cagtcagacagtacacaccg	201
Eryngii18s_1F Eryngii18s_1R	gtgcacgcttcactagtctt gagagccaagagatccggtg	222
Eryngii18s_2F Eryngii18s_2R	caacggatctcttggtctc cccaacaatcaaaccatcac	200
<b>Glucan Synthase</b>		
Shiitake_3F Shiitake_3R	tacctcgaggaatgtctaaag attgtaatactcccgaatgttg	366
Eryngii_3F Eryngii_3R	ctcggaggaatgcttgaaga actgataatattccgagtgtct	361

To address the primer inefficiency, additional sets of primers of *Lentinula edodes* were found from (Reverberi et al. 2004). Partial sequences of shiitake and eryngii were obtained from Genbank AY158742.1 and AY254580.1, respectively. The sequence found was aligned using the blastn algorithm in BLAST. Other additional primers were designed using primer3 with the same conditions. The base pair length of *Lentinula edodes*  $\beta$ -1,3 glucan synthase and *Pleurotus eryngii*  $\beta$ -1,3 glucan synthase is 420 bp and 483 bp respectively.

#### Sample collection

Fresh packs of different types of *Lentinula edodes* and *Pleurotus eryngii* were collected- shiitake, organic shiitake, and eryngii. The mushrooms were purchased at local supermarkets: the conventionally-raised shiitake were from the My Basket in Nishiazabu, Tokyo, and the organic shiitake and eryngii were from the Peacock store in Hamacho, Tokyo. Three biological replicates were taken from each pack.

#### RNA isolation and cDNA synthesis

RNA was isolated using the RNA Plant and Fungi isolation kit (Takara Bio Cat. #: U0949B) as described with minor modifications. Mushroom tissues were homogenized using a mortar and pestle without liquid nitrogen. Ethanol was substituted with isopropanol for the precipitation of RNA. We used 30 $\mu$ l of rDNAse in a buffered solution from the RNA Plant kit to digest the DNA on the column after filtration. 1st strand cDNA synthesized using PrimerScript 1st strand cDNA Synthesis Kit as described (Cat. # 6110A).

#### Semi-quantitative gene expression analysis using RT-PCR

PCR and gel electrophoresis was conducted using the mini16 thermal cycler and bluGel electrophoresis unit from MiniPCR. (QP-1500-01, QP-1016-01)

An amplification curve was created to determine the optimum number of cycles before RT-PCR. Table 1 shows the sequence of the primers used.

All primers had a concentration of 10  $\mu$ M. PCR conditions were as follows: 98°C for 2 minutes of initial denaturation, 98°C for 15 seconds, 60°C for 30 seconds, and 72°C for 1 minute, repeated 24 cycles. Reactions were as follows: 12.5 $\mu$ l EmeraldAmp 2X Master mix, 1 $\mu$ l of cDNA, 0.5 $\mu$ l of forward primer, 0.5 $\mu$ l of reverse primer, and 11 $\mu$ l of dH<sub>2</sub>O. Gel electrophoresis was used for semi-quantitative analysis. Band size was quantified from RAW photos of gels using the ImageJ Bio-Formats plug-in.

TABLE 2: RNA quality for each biological replicate. Samples S1, SO-1, SO-3, and E-2 were used for analysis

RNA isolation				
Sample	A260	A280	A260/A280	Concentration of RNA (ng/l)
Shiitake-1	0.086	0.047	1.829	137.6
S-2	0.067	0.05	1.34	107.2
S-3	0.036	0.029	1.241	57.6
Shiitake organic-1	0.155	0.075	2.066	248
SO-2	0.009	0.011	0.818	14.4
SO-3	0.108	0.006	18	172.8
Eryngii-1	0.042	0.018	2.333	67.2
E-2	0.265	0.082	3.231	424
E-3	0.329	0.169	1.946	526.4

#### Results and Discussion

Based on the results of semi-quantitative RT-PCR, we found that organic shiitake showed the highest expression of glucan synthase, followed by eryngii and conventional shiitake (Figure 1). Organic Shiitake sample 3 showed the highest expression of glucan synthase- 156.1% of the expression of housekeeping gene 18S- followed by Organic Shiitake sample 1 with 69.8%, Eryngii sample 2 with 31.7%, and Conventional Shiitake sample 1

with 0%. There was no glucan synthase expression detected for conventional shiitake although the housekeeping gene was present.

TABLE 3: RNA quality for each biological replicate. Samples: Conventional Shiitake Sample 1, Organic Shiitake Sample 1, Organic Shiitake Sample 3, and Conventional Eryngii Sample 2 were used for analysis.

Sample	Normalized expression of glucan synthase (% of 18S expression)
Conventional Shiitake Sample 1	0
Organic Shiitake Sample 1	69.8
Organic Shiitake Sample 3	156.1
Conventional Eryngii Sample 2	31.7

**Normalized expression of glucan synthase (% of 18S expression) vs Sample**

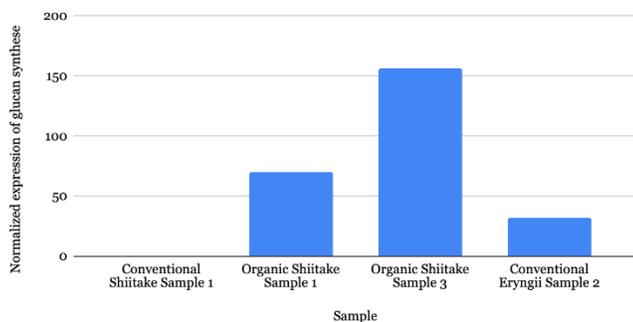


FIGURE 1: Normalized expression of glucan synthase in each sample relative to 18S expression (internal control).

Although this research could not determine the reason, there may be several possible explanations as to why conventional shiitake did not show any glucan synthase expression. First, the difference in fertilizers or pesticides used between conventional and organic shiitake may affect the amount of glucan synthase being

expressed in mature fruiting bodies (Brunner and Freed, 1994). However, mushroom cultivation practices were beyond the scope of this study. Future experiments should include more biological and technical replicates to more fully characterize the possible effect. Second, since the expression of glucan synthase is highest for organic shiitake, it could be the most useful for wound healing compared to the other samples tested. Furthermore, the effect of the expression of glucan synthase in wound-healing could be tested on animal models and synthetic skin (Božena et al., 2017).

Additional testing is required to determine whether the RNA quality was a response to the lack of glucan synthase expression. Also, it was tough finding and designing the primers; several primer pairs were ineffective. The primer efficiency of shiitake and eryngii should be assessed moving forward. If our hypothesis is truly supported by the data- that conventional shiitake does express less glucan synthase- it represents a novel insight into the differences between organic and conventional shiitake.

Even though this is preliminary research, we hope that our work can facilitate a greater understanding of glucan synthase expression found in edible fungi.

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# Systematic review with meta-analysis of fall detection systems for elderly care: perspectives for an aging population in Japan

Wataru Hoshi

Tabor Academy, United States  
wataruhoshi1113@gmail.com

## Abstract

A combination of demographic, social and economic factors are causing an immense strain on the elderly care systems of Japan and other countries with aging populations. Advances in automation offer promising means of reducing labor costs while also improving the lives and privacy of those in care. Here, we aim to analyze the feasibility of automatic fall detection systems for the elderly, gain an understanding of the current status of fall detection and its possibilities, and finally, examine the steps necessary to overcome current limitations. Using systematic review methods, papers were searched in PubMed and screened based on inclusion and exclusion criteria. Seven papers were used to create a quantitative synthesis. There was a large variation of fall detection methods that used wearable, ambient or both types of sensors, combined with unique algorithms to interpret whether a fall has occurred. The difficulty in ethically and safely using elderly people as subjects remains an issue in fall detection tests. The lives of our grandparents, parents and eventually ourselves can be saved through the development of this technology.

## Introduction

Japan is a prime example of a country facing the issue of an aging population caused by decreasing birth and death rates. According to the Statistics Bureau of Japan (2020), it has

quickly surpassed nations such as Germany and Italy in percentage of elderly citizens and has one of the world's highest mean ages. The proportion of people aged 65+ surpassed the child population since 1997 and made-up 28.4 percent of the population in 2019 (Statistics Bureau of Japan, 2020). Not only is the elderly population growing, but so is the demand for care workers. By the end of fiscal 2025, 550,000 additional care workers are predicted to be needed (Yasuo, 2020). Combined with the high stress and low pay of the job, it is not surprising that a shortage of elderly care workers exists as a major problem in the nation.

A variety of new technologies have been developed with a wide range of utility all designed to relieve the strain on the elderly care systems by decreasing the need for labor through automation while also improving the lives of those in care. With the growing advancements in home automation, new monitoring systems strive to keep senior citizens safe in their homes or care facilities without the constant attention of a human caretaker. There are attempts to both integrate technology with existing items, such as beds and walking frames, as well as to create new devices such as braces to assist in movement. Medicine dispensing and routine health checkups are increasingly done by automatic and digital systems. The social interaction and companionship that many care workers provide is often overlooked, but researchers have

attempted to automate the inherently complex human factor of elderly care. There are several robots that try to simulate the emotional care that these workers do with varying success including Paro and Pepper (Foster, 2018). That said, automation in elderly care is still far from reaching its full potential and achieving widespread adoption.

As people age, their decline in sensory, physical and cognitive abilities can often lead to falls that can cause serious injury or even death. According to the Center for Disease Control, falls are the most common cause for traumatic brain injuries and are the cause of 95% of hip fractures. Up to three million older people are treated in emergency departments for injuries caused by falling every year (Center for Disease Control). This statistic will continue to rise as the elderly population increases and existing healthcare systems struggle to keep up. Combined with the undermanned status of many care facilities, utilizing some form of logistically and financially viable and effective fall detection system becomes imperative to saving lives. Here, we conduct a systematic review to provide a deeper understanding of the potential and limitations of automated fall detection technologies in elderly care.

There are a few ways fall detection systems have been engineered. One type is the wearable fall detectors which utilize sensors such as accelerometers and gyroscopes by having the user carry or wear it in some form. The combination of increased electronic device ownership (in the form of phones and smart watches) as well as more affordable, smaller and effective sensors mean that the potential for these fall detection systems are rising. However, many of these items such as vests and belts can be intrusive and restrict movement. Because these systems require the user to consistently have them equipped and do so on their own volition, any discomfort is detrimental to its ability to do its job. Another obvious issue is battery life. Since users may be unable to recharge any devices for a multitude of reasons or just simply forget to, the

length of battery life must be maximized, and the complexity of charging simplified to reach a point of viability. Ambient systems can overcome some of these issues. By using various sensors such as infrared and pressure mats to observe the movement within a room, algorithms can detect when a fall has likely happened. They do not encumber users and require little to no interaction to work. However, ambient systems have their own flaws. Unlike wearable sensors, the location/area that these systems are effective are limited to closed spaces with as little interference as possible. Observation systems can also be a major source of privacy concern.

By utilizing a systematic review with meta-analysis, we aim to gain an understanding of the design and technology used in fall detection systems, as well as their varying capabilities. Simultaneously, through the categorization of the detection type, we can determine the most effective strategies and technologies for fall detection. Due to the simpler design, we hypothesized that wearable fall detection systems would perform better than ambient ones.

## **Method**

### *Search Methodology*

To collect the papers on this topic, a search engine called PubMed was utilized. PubMed searches the MEDLINE database, which includes references and abstracts in the fields of life sciences and biomedicine. The search terms “elderly care”, “senior care” were used in conjunction with “fall detection” and “fall recognition”. Citations were exported from PubMed and organized using Zotero, a reference management software. Each group of results were scanned separately for relevance using the title; the abstract was used when necessary due to any ambiguities regarding the paper’s research objectives. Duplicates were removed after combining the remaining papers. This search was done between the dates of August 2nd and 19th, 2021.

### *Inclusion and Exclusion criteria*

Only papers published in English were included. Papers that included tests of fall detection systems were selected. From these, papers that reported one or more of accuracy, sensitivity, or specificity as outcomes were used. Since the focus of this study is on automatic fall detection, papers on fall prevention and prediction systems were excluded. In order to have a standard form of measurement for the effectiveness of the various fall detection systems, accuracy, sensitivity and specificity were chosen. It is relevant to note that many papers included some but not all three of these measurements.

### *Data extract and analysis*

Data such as the number of participants, accuracy, sensitivity, and specificity were organized into a spreadsheet. The data from a paper were divided into subcategories when appropriate, such as when different types of a detection system was used.

We initially planned to use the Downs and Black (1998) quality assessment checklist; however, many of the questions did not fit the type of trials conducted in the papers used. Instead, in order to weigh in the quality of the data, the papers were assessed (a scale of 0-5) on how representative the participants in the trials were compared to actual senior citizens that would be using these interventions. This was based on a Downs and Black (1998) quality assessment checklist question "Were those subjects who were prepared to participate representative of the entire population from which they were recruited?". Papers that used subjects closest to the elderly population (60~ years old) were given a 5 while papers that did not use any real people were given a 0.

The weight of a paper's data was calculated by multiplying the number of participants with the quality assessment score. The accuracy, sensitivity and specificity percentages of each paper was multiplied by this weight. The results of

this were added together and divided by the sum of all weight values to get the weighted average.

Definition of Accuracy, Sensitivity and Specificity:

$$\text{Accuracy} = \frac{(\text{true positive} + \text{true negative})}{(\text{true positive} + \text{false positive} + \text{true negative} + \text{false negative})}$$

$$\text{Sensitivity} = \frac{\text{true positive}}{(\text{true positive} + \text{false negative})}$$

$$\text{Specificity} = \frac{\text{true negative}}{(\text{true negative} + \text{false positive})}$$

### **Results**

Through the initial search, 190 papers were found, 64 of which passed the screening for relevance to the topic. Out of these papers, 7 were removed as duplicates. Afterwards, 45 of the 57 were excluded because they did not include data from trials/tests. Of the 12 left, 4 did not use the measurements of either accuracy, sensitivity or specificity and were excluded as well. Of the remaining papers, 1 did not use real people for trials and was excluded from the quantitative synthesis. The final number of papers used for meta-analysis was 7.

The average number of participants was 18.1 people; the greatest number of participants was 50 and the lowest was 0. The paper with 0 participants relied on computer-simulated falls to measure accuracy, sensitivity, and specificity of a virtual ambient fall detection system. The years the papers were published ranged from 2008 to 2020. The average year of publication was 2014.

TABLE 1: Qualitative Summary of Papers Included in Meta-Analysis

Author and year	Type of intervention	Number of participants	Quality assessment (0-5)	Summary of outcomes Accuracy, Sensitivity, Specificity
System Design for Emergency Alert Triggered by Falls Using Convolutional Neural Networks (2020)	Ambient fall detection system that utilizes low-resolution infrared sensors. Tested with 3 types of recurrent neural networks (LTSM, GRU, Bi-LTSM).	4	3	LTSM: 91, 89, 93 GRU: 87.5, 85, 89 Bi-LSTM: 93, 93, 93
SisFall: A Fall and Movement Dataset (2017)	A wearable self-developed belt device that utilizes an accelerometer to detect falls.	38	3	Young: 92.684, 95.74, 89.624 Elderly: 88.112, 79.446, 96.76
Validity of a Smartphone-Based Fall Detection Application on Different Phones Worn on a Belt or in a Trouser Pocket (2015)	Smartphone based fall detection that uses built-in accelerometer. Algorithm to generate fall alarm from data. Samsung S3 and S3 mini were worn in belt or trouser pocket.	8	2	Phone on Belt 3: N/A, 75, 97 Phone on Belt 3 mini: N/A, 90, 99 Phone in Pocket 3: N/A, 90, 87 Phone in Pocket 3 mini: N/A, 88, 91
Simulated Unobtrusive Falls Detection With Multiple Persons (2012)	Simulated ambient fall detection system based around the capabilities of a dual-technology sensor (DTS).	0	0	Two Motion Detectors: 93.33, 100, 85.71 One Motion Detector: 66.67, 50, 87.71
TESTING OF A LONG-TERM FALL DETECTION SYSTEM INCORPORATED INTO A CUSTOM VEST FOR THE ELDERLY. (2008)	A tri-axle accelerometer, microprocessor, battery, micro-SD card and Bluetooth module incorporated into a wearable vest.	10	4	N/A
Self-Adaptive Fall-Detection Apparatus Embedded in Glasses (2012)	Glasses with integrated apparatus that uses a tri-axial magnetometer, accelerometer and gyroscope to detect falls.	50	2	System Without Adaption: 90.7, 79.8, 97.7 System With Adaption: 92.1, 81.7, 98.7
GAL @ Home (2012)	A fall detection system that combines an on-person tri-axial accelerometer and an optical Imagine Source sensor.	7	2	N/A, 91.35, 95.00
An Energy-Efficient Fall Detection Method Based on FD-DNN for Elderly People (2020)	Wearable fall detection system that uses a tri-axial accelerometer and gyroscope with a focus on low power.	38	4	FD-DDN: 99.17, 94.09, 99.94 LSTM: 96.88, 81.47, 99.57 CNN: 98.13, 87.5, 99.88
Evaluation under real-life conditions of a stand-alone fall detector for the elderly subjects (2011)	The Vigi'Fall has the user attach a micro-sensor at thorax level which works in conjunction with peripheral inferred sensors.	8	5	N/A, 62.5, 99.5

Table 1 provides a qualitative summary of the seven papers included in the meta-analysis.

Sucerquia, López and Vargas-Bonilla (2017) tested a fall detection system based around an accelerometer that is worn on a belt. A gyroscope was included in the design but was not used in the data that was collected. This study was conducted with 38 people (15 elderly). The elderly people in this study only performed physically

undemanding and non-fall events except for a singular Judo expert. This person and the group of young adults performed both the ADL (activities of daily living) and falls. The algorithm was trained with (93% accuracy, 96% sensitivity, 90% specificity) and without data from elderly people (88% accuracy, 79% sensitivity, 97% specificity). To take advantage of the growing use of smartphones and their capabilities, Vermeulen et al. (2015) tested a smartphone-based fall detection system that utilizes the built-in

accelerometers and processing power. As pointed out by the author, a smartphone device removes the need to buy new equipment while also reducing the stigma of using the device by using something already familiar. The trials specifically used the Samsung S3 and S3 mini on a belt and inside a pocket. Eight healthy adults were used in this study and accuracy was not measured. The test with the phone on the belt had a sensitivity of 75% and specificity of 97% with 90% and 99% for the Samsung S3 mini. For the tests with the phone in a pocket, sensitivity was 90% and specificity of 87%. The mini had 88% sensitivity and 91% specificity.

Gietzelt et al. (2012) combines a wearable tri-axial accelerometer with an ambient optical sensor. To make the tests more realistic for the vision sensors, “different illumination conditions were integrated in the test scenarios”. The tested sensitivity was 91.35% and the specificity was 95%. Only the pre-study results were used for the quantitative synthesis. However, it is noteworthy to mention that when this system was tested outside of a laboratory environment, the vision sensor faced issues due to its limited view. The optimal location to place it was difficult to find and the falls took place outside of the view of the camera or were undetected due to poor lighting.

mean. Specifically, Bloch et al. (2011) had a 62.5% sensitivity while Ariani et al. (2012) had a 50% sensitivity. There were no clear trends between the characteristics of each paper, such as publication date and the type of intervention, and values for percent accuracy, specificity, and sensitivity.

### Discussion

Although the final weighted accuracy values are high, it is important to keep in mind that performance expectations must be high given the repercussions of a faulty reading. The data from the quantitative synthesis conducted suggest that there are capable fall detection systems but require further and more thorough testing before any efforts to properly implement them.

Despite initial assumptions, there was not a positive relationship between how recent the paper was published and the effectiveness of the fall detection system. However, given the lack of standardized trial methods and different types of intervention, there is not necessarily a stagnation in fall detection technology. Similarly, there is no correlation between the number of participants and the years of publication, suggesting a lack of large-scale increase or decrease in efforts to test fall detection systems.

Additionally, there was no correlation observed between the type of intervention (specifically wearable compared to ambient) and effectiveness. My initial assumption was that ambient fall detection systems would perform worse due its more complicated design, but this hypothesis was not supported by our findings.

There are a few things that suggest that these fall detection systems would have performance issues when used in an actual non-trial environment. Many devices had reliability issues ranging from sensor malfunctions to battery death during testing that are not manifested in the data collected. For example, Gietzelt et al. (2012) conducted a follow up experiment to a pre-nup study where they had 3 elderly patients equipped with fall detection systems for a period of time (separate to the data included in the quantitative

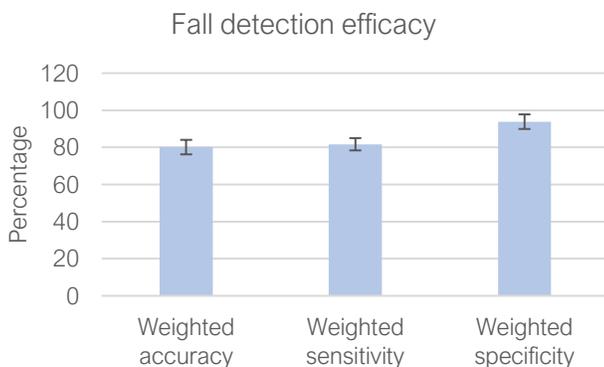


FIGURE 2: Fall detection efficacy.

Figure 2 shows the outcome of the meta-analysis. The final weighted accuracy, sensitivity and specificity were 83.34, 82.44 and 93.6 percent, respectively. Most trial results ranged from 80~99% aside from two outliers well below the

synthesis). Two falls out of nine that occurred during this investigation were correctly detected. This is significantly worse than the results from the pre-study that utilized the same system and suggests that the percentages of many of these studies conducted may be deceiving.

Due to the difficult nature of simulating a real fall of an elderly person while ensuring people's safety, many of the papers had to emulate them with fake falls from younger people to collect data. Depending on how this issue was resolved, differing amounts of inaccuracy will exist in the measurements of fall detection system effectiveness. In our study, we attempted to mitigate the differences by incorporating the quality assessment into the weight average calculation. However, the scarcity of actual elderly subjects may nevertheless cause inaccuracies in the results. Older people fall differently than younger, healthier, and more physically stable people.

While we hope that this systematic review provides a fuller understanding of fall detection systems in elderly care, there are a number of limitations to our findings. Differences in methodology and environment of the trials conducted were not accounted for in this analysis. Some of the data may be more accurate than others due to a higher quality of trial methods. The grading of quality using the question "Were those subjects who were prepared to participate representative of the entire population from which they were recruited?" with a scale from 0-5 is somewhat subjective and based on the judgment of a singular person. The search was unfortunately limited to only PUBMED because other electronic databases were unavailable or inaccessible. This limited the number of relevant papers and possibly excluded valuable data that may have given a better idea of fall detection efficacy.

## Conclusion

With recent advancements in fields such as sensor technology and artificial intelligence, the potential for fall detection systems are ever-growing. The systematic review showed that several successful methods for fall detection have been developed. However, several steps are necessary for fall detection systems to reach this full potential and achieve widespread adoption. More emphasis must be placed on conducting studies with higher numbers of real elderly subjects in realistic environments to properly understand their capabilities and limitations. Furthermore, many these will likely require varying degrees of improvement in reliability, affordability and comfort before they are practical and realistic for any large-scale distribution. Countries such as Japan that are already facing overburdened elderly care systems caused by an aging population should increase their research and investment into developing and distributing an effective fall detection system.

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# Disparities in Access to Primary Dental Care: A Systemic Review

Christopher Huang  
The Westminster Schools, United States  
christopherhuang@westminster.net

## Abstract

Primary dental care is essential for the maintenance of health and wellbeing. Aside from maintaining the state of teeth for matters of appearance, primary dental care prevents the development of more severe health issues down the line. Furthermore, dental conditions are generally more relatively preventable, compared to other conditions that have chronic effects on health. This further highlights the importance of access to primary dental care. However, in America, numerous barriers exist in attaining a level of care needed for the prevention of dental conditions. Socioeconomic disparities account for a large barrier to care, as the cost of dental visits surpasses the perceived value of the visit for some patients. Geographic barriers also limit access if there are transportation or distance issues. Furthermore, examination of demographic factors including race, gender, and educational attainment reveal more trends in access and use of primary dental care services. In addition, the interactions of these factors and considerations of intersectionality are crucial in obtaining a clear picture of dental disparities.

This paper seeks to address the question: "How do differences and interactions between socioeconomic, geographic, and other demographic variables affect access to primary dental care?" By examining existing disparities and their root causes, insight can be gleaned about possible ways to coordinate more targeted public health action to minimize these differences and expand access to primary dental care.

*Keywords: Primary Dental Care, Public Health, Dental Disparities, Socioeconomic Factors, Demographics*

## Introduction

Dental care is predominantly an aspect of primary care, as individuals within a community often see dentists in an outpatient setting for simple procedures or preventative care (Morris & Burke, 2001). Consequently, dental care is one frontline aspect of maintaining health and wellness within a community. Furthermore, sufficient dental care is crucial for the prevention of multiple conditions, including tooth loss, oral cancers, and tooth decay, which have lasting impacts on health. Globally, oral diseases are some of the most common diseases, despite their relatively preventable nature. They incur health burdens as quality of life is disrupted, with effects ranging from pain that interferes with functioning to sepsis. The importance of dental care makes it even more important to examine the reasons why dental care is insufficient in certain populations, leading to disparities in disease prevalence and overall health and wellness.

It is also important to recognize that patterns in the prevalence of dental conditions illuminate certain barriers to care; for instance, children in poverty, socially marginalized groups, and older individuals disproportionately feel the burden of dental diseases and experience insufficient access to dental care (Peres et al., 2019). The fact that the prevalence of preventable dental

conditions has remained high, especially in countries with lower income, highlights the barrier posed by the cost of dental treatment. Because of this inherent obstacle, advancements in dentistry may not be as useful on a larger scale if socioeconomic hurdles are not addressed.

In America, the pattern of unmet need due to certain disparities is likewise reflected. Barriers also prevent a large portion of the United States of America population from adequate preventative dental care, despite how prevention is easier and less expensive than treatment if any problems arise (Vargas & Arevalo, 2009). Socioeconomic problems present major obstacles to care. Aside from financial barriers, many other demographic variables lead to dental care disparities. In this paper, the factors examined consist of socioeconomic status, geographical location, race, gender, and educational attainment. These can affect different aspects of visiting a dentist, from not being able to physically visit due to time or geographic constraints, to not being able to afford dental care if it is physically available. In addition, social capital and health literacy are also considerations. Some possible barriers to treatment are illustrated in Figure 1. These barriers may be stronger or weaker for individuals depending on the aforementioned variables and possibly other factors. In addition, the interactions of these factors and considerations of intersectionality are crucial in obtaining a clear picture of dental disparities. Some of these factors may compound, heightening disparities disproportionately in certain population subsets. Both controlling for factors to isolate variable effects and examining the overall picture with the interplay of variables could be helpful, as one reveals correlational effects more strongly while the other is more reflective of the real world.

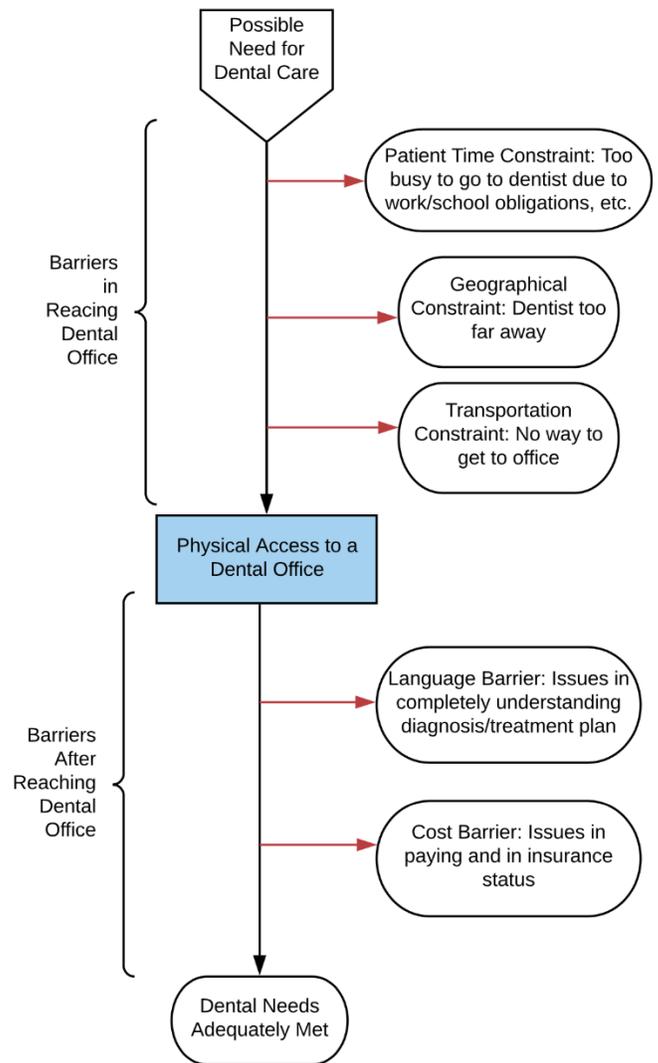


FIGURE 1: Possible Barriers to Accessing Primary Dental Care

History has pointed towards there being effective strategies for improving dental health for the broad population. The reduction in the prevalence of dental caries via community tap water fluoridation (with about 75% of those with community water supplies receiving optimally fluoridated water), has been widely hailed as a modern public health achievement in the USA (Allukian et al., 2018). Despite this success, there are still issues that need to be addressed, such as the high prevalence of preventable dental caries and periodontal disease (Northridge, Kumar, & Kaur, 2020). Regarding existing public health

initiatives targeting dental care, oral conditions are highlighted by the Healthy People 2030 objectives. These objectives include those seeking to minimize disparities, such as increasing the proportion of the population with dental insurance and decreasing the percentage who could not access necessary dental care from 4.6% reported in 2017 to 4.1% by 2030. Further minimization of disparities is essential for achieving equitable healthcare in the USA.

## Methods

To find publications concerning disparities in dental care, the Medline database was searched for English-language literature that addressed existing disparities in primary dental care, along with publications suggesting possible solutions. To review relatively recent public health studies, only papers from the past twenty years were reviewed. In addition, only studies that examined dental trends in America were selected. A broad search was first conducted using the phrase “dental disparities.” After reviewing recent publications in this category, a set of recurring factors accounting for disparities was determined. These were socioeconomic status, geographical location, race, gender, and educational attainment. To further review these specific categories, searches were targeted towards dental disparities depending on those factors. For example, the search term “socioeconomic dental disparities” was used to delve into publications relating socioeconomic inequalities with disparities in dental care. Overall, a total of 27 publications were reviewed for information concerning data and trends for dental care disparities and possible solutions to them.

## Results

### *Socioeconomic Factors*

Socioeconomic issues stand out as a key obstacle to adequate dental treatment, as a 2014 survey after the implementation of the Affordable Care Act in America revealed that across different categories of age, income, and insurance status,

dental care had a disproportionately high financial barrier compared to other types of healthcare (Vujicic, Buchmueller, & Klein, 2016). One important aspect in overcoming financial barriers is insurance coverage. Medicaid provides insurance coverage for low-income Americans, and recent expansions in dental care for Medicaid in 2014 were projected to increase the chance of dental visits within a year by 16.4-22% (Choi, 2011). Retrospective data showed that Medicaid expansions increased the likelihood of dental visits by over 10% in 2016, compared to before the expansion took effect. In the state of Oregon, after Medicaid expansion of dental care, the percentage with unmet dental needs dropped by 13.5%, although it did not affect the rate of use for any dental services not covered under Medicaid (Baicker, Allen, Wright, Taubman, & Finkelstein, 2018).

Despite coverage improvements, disparities are still evident – the same study that reported an increased rate of dental visits in 2016 also noted this change was mainly in states with high dentist concentrations – areas with fewer dentists saw no dental visit rate improvements (Wehby, Lyu, & Shane, 2019). There are still significant gaps in met need across socioeconomic groups: in the state of Georgia, 59% of need was met for low-income children, compared to 96% for high-income children (Cao, Gentili, Griffin, Griffin, & Serban, 2017). Another study from Florida discovered that although for both Hispanic and non-Hispanic patients, emergency dental care at hospitals was most often covered by Medicaid, current Medicaid coverage alone would not adequately bring equity in terms of high-quality dental care (C. A. Serna, Arevalo, & Tomar, 2017) (Demby & Northridge, 2018). Dentist participation in public insurance also matters as the median met need in Georgia increased from 30.5% to 100% as projected provider acceptance of Medicaid rose from 20% to 80% (Cao et al., 2017). Indeed, Medicaid’s “low and inconsistent reimbursement rates” contribute to dentists

rejecting Medicaid. Compounded with the payment factor is that patients of lower socioeconomic status might experience more difficulties taking time off work to visit a dentist, or have transportation challenges (Patrick et al., 2006).

The repercussions of unmet dental care have led to a higher prevalence of dental conditions, such as untreated dental caries. For instance, low-income respondents in the US on average have double the prevalence of mild to moderate untreated caries (26.2% compared to 13.2%), and 2-3 times higher prevalence of severe untreated caries. In addition, publicly insured low-income adults still had a 20.5% prevalence of mild to moderate untreated caries, while privately insured adults had a prevalence of 13.3%, showing a gap in public insurance coverage (Williams, Wei, Griffin, & Thornton-Evans, 2021).

Overall, socioeconomic disparities are very significant when it comes to dental care. Among Americans with unmet dental need, 78% cited the inability to afford dental care accounted for 78%, and the same study found that low-income adults reported unmet dental care three times more frequently than higher-income adults (Williams et al., 2021).

### *Geographic Factors*

Aside from purely the cost aspect of dental care being a hurdle with those of lower socioeconomic status, issues often arise with difficulties in finding reliable transportation, compounded by the time it takes to see a dentist (Patrick et al., 2006). Transportation factors, availability of dental care, and convenience of visiting a dentist are encompassed by geographic factors. Commonly, this most prominently affects low-income populations with transportation barriers and rural populations where there are fewer dentists.

Regarding transportation, cost of transportation and access to regular transportation is a

significant concern. Data from the Iowa Dental Wellness Plan revealed that 11% of respondents noted that transportation problems accounted for unmet dental need. In the model, travel distance was not correlated with a significant difference in dental care usage, but rather cost of travel had a significant negative correlation with dental care utilization (McKernan et al., 2018). A study from Georgia found travel distance disparities across urban and rural populations: while the average travel distance to dentists was 3.7 and 17.2 miles for high and low income children respectively, and these values increased to 11.6 and 32.9 miles for high and low income children in exclusively rural areas (Cao et al., 2017).

Furthermore, rural populations are affected by other public health dental care disparities, including lower dental care utilization, higher prevalence of dental caries, less fluoridated water supplies, greater travel distances, fewer dentists per capita, and increased travel distances to dentists (Skillman, Doescher, Mouradian, & Brunson, 2010). Rural populations also have less access to hospital-based dental care (Harrison, Daniel, & Nemecek, 2007). Overall, these issues reveal a significant disparity, towards which public health policy should be directed to mitigate these differences between rural and urban dental care.

### *Racial Factors*

Racial factors also contribute to disparities in dental care, even when demographic and socioeconomic variables are accounted for. For instance, in the US, older black patients had a significantly higher prevalence of decayed teeth compared to older white patients after controlling for other socioeconomic/demographic factors (Liang, Wu, Plassman, Bennett, & Beck, 2013). In addition, non-Hispanic whites in America are the most likely to receive annual dental exams, which are a key aspect of preventative primary dental care (Horner-Johnson, Dobbertin, & Beilstein-Wedel, 2015). Within specific geographic areas, disparities can be seen: compared to their rural

white counterparts, rural African American populations had significantly more tooth loss even if there was a stable source of health care. Overall, rural African American populations show a 28% rate of tooth loss and 34% rate of dental visits, which are high and low proportions respectively (Caldwell, Lee, & Cagney, 2017). For comparisons within public insurance, Latino and African American children report longer intervals between dental visits compared to white children on Medicaid. This same trend is reflected within private insurance, with African American and Latino children visiting dentists at a lower rate than white children (Pourat & Finocchio, 2010).

Meanwhile, other studies have found that certain other variables make a difference in racial disparities in dental care and controlling for these makes the differences statistically insignificant. One study noted that enabling “resource variables” including income level, insurance, census region, and metropolitan statistical area, make the difference in utilization in dental services between whites, African Americans, Mexican Americans, and other race/ethnicity groups no longer significant. The study, from 2003, found no significant difference between utilization of dental services for racial groups when they are all privately insured. The only statistically significant differences reported in the study were between privately insured whites with publicly insured whites, Mexican Americans, and other race/ethnicity groups (Doty & Weech-Maldonado, 2003). This disparity is not necessarily because of a lack of perceived need for dental care – one study found that only 20.5% of Hispanic migrant farmworkers visited a dentist in the past year, while 61.2% reported they believed their mouths were in poor condition (Claudia A. Serna et al., 2020).

One study studying the differences in dental care across racial groups compared data from 2001 and 2016. It found that for children, prevalence of dental care use increased from [31.4%, 33.3%,

38.1%, 56.8%] in 2001 to [44.1%, 50.7%, 55.2%, 59.8%] in 2016 for African American, Hispanic, Asian, and white children. This indicated that all groups except for African American children reached 49% dental care use, the Healthy People 2020 goal threshold. This shows a significant difference in absolute disparities for all groups, but the change in disparity was lowest for African American children (Robison, Wei, & Hsia, 2020).

Overall, racial disparities regarding primary dental care in the US should be studied more in-depth. Controlling for certain factors may or may not lead to statistically significant differences in different markers in oral health and access to quality primary dental care. As previously stated, controlling for certain markers helps to form a stronger correlation and clarify certain problems, but other times overall outcome and the convergence of many factors should be taken holistically as that is reflective of real life. However, some studies show trends that have pointed towards a narrowing of racial disparities over the past years.

### *Gender Factors*

Gender disparities in dental care are nuanced and reveal areas where public health intervention can be focused. Men tend to have poorer oral health, which can be attributed to behavioral factors, including increased tobacco/alcohol use, and biological factors, including hormone and immune system differences. Public health interventions can help target the behavioral aspects. Overall, men ignore their oral health and have poorer oral hygiene habits. This is associated with men reporting more negative attitudes about dental visits and less oral health literacy (Lipsky, Su, Crespo, & Hung, 2021).

Conversely, women encounter financial barriers to dental care more often, as one study noted that 15% of men and 20% of women “did not receive dental care due to cost.”

When assessing access to dental care, approximately 20% of women, as opposed to 15% of men, “did not receive dental care due to cost” (Ioannidou, 2017).

### *Educational Factors*

Differences in educational attainment are also associated with disparities regarding dental health care. Obtaining education above a high school diploma (over 12 years of education) was correlated with a lower number of missing teeth, lower prevalence of dental decay. Even after controlling for demographic variables of age, gender, and race, the difference was still statistically significant. Compared to the rate of tooth decay for those obtaining more than 12 years of education, the risk ratios were 2.45 and 1.84 respectively for those who did not get a high school diploma and those who had no education beyond a high school diploma. The rates of use of dental sealants were higher in those who had more than 12 years of education compared with less than 12 years of education (4.9% and 4.6% in 2005–2006 and 2007–2008, respectively) (Liu, Li, & Walker, 2014). In addition, high education attainment was associated with both a lower probability of poor oral health and better self-rated oral health (Assari, 2019). The question remains of to what extent these educational effects are associated with other variables, such as financial status, or if these educational effects are more direct, such as having an impact on dental health literacy.

### **Discussions**

Reviewing studies examining disparities in primary dental care has revealed many overarching trends. Overall, socioeconomic and insurance challenges pose major barriers to patients seeking quality dental care. Disparities between Medicaid and private insurance can be targeted by public health policy, and previous evidence has shown that expansions for dental care in Medicaid has helped decrease unmet dental care need. Lower income is still associated

with reduced access to primary dental care, but reforms could help bridge the gap in dental care access in lower versus higher class households.

Furthermore, rural populations have less accessible dental health care than urban populations. Racial disparities suggest that white Americans have the highest levels of dental utilization, although controlling for certain economic variables decreases this disparity in one study. Gender factors suggest women have improved oral health due to better health literacy and attitude towards dentists, as well as a lower rate of smoking and alcohol consumption, but women also face financial barriers to dental care more often. Finally, educational attainment over a high school diploma is associated with better dental outcomes.

With these findings, it is important to note that these are not all the possible factors leading to disparities and that the interactions between variables may compound or mediate certain effects. For example, having a disability is another factor that leads to patients being unable to receive needed dental care. This effect is further compounded for disabled individuals in underserved racial groups – one study found this was especially prominent for American Indian, Alaska Native, and multiracial individuals, as they had fewer receipt of examinations, delays in obtaining care, and more cases of not receiving needed care (Horner-Johnson et al., 2015).

Accounting for the compounding effect of multiple variables provides information to implement public health policy more effectively. While looking at individual variables gives a more simplified picture where correlations can be clearly drawn, it is important to realize that people in real life have many interacting factors that affect their access to primary dental care. Healthcare research has shifted towards a more intersectional lens of analysis, but many dental studies still focus narrowly on certain variables and note other

factors as “confounders” instead of examining intersections. For example, one study analyzing the impact of racial discrimination on dental care separated gender, race, and ethnicity as “confounders” rather than studying the combination of variables (Elaine Muirhead, Milner, Freeman, Doughty, & Macdonald, 2020). Indeed, literature commenting on intersectionality and access to dental care is sparse. However, when expanded to healthcare literature in general, important intersectionality studies have insights that might be applied and further studied in dentistry. For instance, a study on low-income African American women found the intersection created a healthcare environment of stereotypical assumptions and discriminatory practices. The intersection of identities led to interactions with healthcare providers that resulted in issues including a need for patient self-advocacy to have their concerns addressed and provider disregard for patient preferences (Okoro, Hillman, & Cernasev, 2021). Because the discussed demographic variables are not mutually exclusive, multiple combinations of them could be studied to see what unique issues occur due to intersectional identities, and how they impact access to primary dental care. Thus, solutions to disparities in dental care should seek effective change while accounting for how individuals are multi-faceted.

### **Conclusions**

Multiple disparities exist within access to primary dental care and dental outcomes. With future research and improvements in public health policy, these disparities can further lessen. Public health research so far does address the role of multiple disparity factors such as the effects of income, race, insurance, and geographic factors as thoroughly as needed. In addition, these disparities should be marked with multiple indicators aside from just dental utilization, including the quality of the care itself (Northridge et al., 2020).

Through researching these disparities and targeting policy, outcomes can be improved. Medicaid expansion for dental care has already been shown to improve dental care utilization (Baicker et al., 2018). Transportation barriers can also be addressed to help low-income individuals, such as improved public transport (McKernan et al., 2018). For example, because access to a dentist might be challenging based on time, cost, or transportation, dental basics being incorporated as part of primary care clinicians’ patient education might help. Family physicians could improve dental health literacy through basic counseling, and basic dental health evaluations could help individuals who usually do not see a dentist as a separate health trip (Stephens, Wiedemer, & Kushner, 2018). Especially for rural areas, mass solutions such as increased water fluoridation and increased dental health curriculum, or implementation of dental mobile clinics or telehealth screening could improve dental health and provide additional points of access aside from formally visiting an established hospital or dentist’s office (Skillman et al., 2010). Granted, a limitation to policies that reduce barriers is the willingness of individuals to change their dental habits even after barriers are lowered. A study of rural teens in Washington state showed low response to efforts made by researchers to reach out and encourage dental care interventions. Conversely, emancipated teens and young adults under 26 engaged with the same offers by researchers at a much higher rate, showing inherent willingness to seek dental care is key even with lowered barriers (Weinstein, Coolidge, Raff, & Riedy, 2009).

A model of more community health centers for rural areas could also lower barriers to dental care (Nycz, Acharya, & Glurich, 2020). However, there would have to be research to create models for sustainable rural dental clinics, as rural hospitals have been closing at an increasing rate, suggesting healthcare institution challenges in rural areas. Some of these closures can be

attributed to changes in policy, which should be re-examined to ensure sustainable rural healthcare systems (Balasubramanian & Jones, 2016). Finally, encouraging dental students from rural areas through loan programs and increased recruitment could help rural disparities, as dentists from rural areas are about six times more likely to practice rurally compared to urban students (McFarland, 2012).

All these solutions do incur costs and could face political opposition, as many public health efforts require government involvement and shifts in budgets, creating another limitation. For instance, opposition to government involvement regarding healthcare has undermined the perception of Medicaid (Dalen, Waterbrook, & Alpert, 2015). This could affect the use of public health insurance in certain states, as some have opted out of Medicaid expansions. However, narrowing disparities and improving the overall access to dental care in the United States could help prevent diseases that could have much more costly repercussions if left untreated.

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# How Does Graft Versus Host Disease React to the Heart, Lungs, and Liver After an Allogeneic Stem Cell Transplant?

Areeba Inam

Strathcona Composite High School, Canada  
areebainam5@gmail.com

## Abstract

E. Donnell Thomas performed the first allogeneic transplantation in 1957. Since then, the field has grown and evolved all around the world. Allogeneic transplantation has become much more accessible thanks to the utilization of matched unrelated donors, umbilical cord blood units, and partially matched related donors. (Henig I. et al, 2014) Research in stem cells has helped doctors and scientists increase their understanding of how disease occurs, the process behind regenerative medicine, and testing drugs for safety. Over a million individuals have benefited from stem cell transplants for the treatment of leukemias, anemias, and immunodeficiencies around the world. (Dulak J. et al, 2015) On the other hand, disease relapse and graft-versus-host disease remain to be the two leading causes of death. (Henig I. et al, 2014) In this systematic review, the effects of graft-vs-host-disease were looked at and how it affected the heart, lungs and liver. When an allogeneic transplant occurs there is a chance for the body's tissues to view the donor tissues as foreign and attack them. The body is a complex and intricate system, when tissues are fighting off what they perceive as threats, at the same time it is harming other organs. (n=26) sources were evaluated and used to assess these effects.

*Keywords: graft-versus-host-disease, allogenic, stem cell, organs*

## Introduction

Stem cells, in simple terms, are the body's raw materials. All cells with specialized roles are created from stem cells, which are the body's basic resources. When stem cells are given the correct conditions in the body or lab, they can multiply and produce daughter cells. The new daughter cells that are made can either become new stem cells or for more specialized cells, ones with specific functions. These include brain cells, blood cells, heart muscle cells or bone cells. Stem cells are the only cells in the body with the ability to generate new types of cells. (Dulak J. et al, 2015) Stem cells can originate from different places, three of the main sources are embryonic stem cells, adult stem cells, and perinatal stem cells. Pluripotent stem cells, also known as embryonic stem cells, come from embryos that are three to five days old. These types of cells can become a type of cell in the body or divide into more stem cells. Most adult tissues, such as bone marrow and fat, contain a limited amount of adult stem cells. They are more limited to various cells of the body. Adult stem cells can create bone or heart muscle cells as well as blood cells. Perinatal stem cells have been found in amniotic fluid and umbilical cord blood, these cells can specialize

into other types of cells. (American Cancer Society, 2021).

#### *Autologous and Allogeneic Stem Cell Transplant*

There are two main methods of stem cell transplant: autologous transplant and allogeneic transplant. Autologous transplant uses cells from the body and allogeneic transplants use cells from a donor. In an autologous transplant, high doses of chemotherapy or radiation are given after stem cells are removed. Once that happens, stem cells are put back in the body to make normal blood cells, also known as rescue transplants. (The Mayo Clinic, 2020) An allogeneic transplant is similar, but instead, the stem cells are donated from a healthy person, the donor. After high-intensity chemotherapy or radiation — a conditioning treatment — donated stem cells from either a related or an unrelated donor are transplanted into the recipient. The conditioning treatment is used to kill any cancer cells that remain in the body, weakening the patient's immune system and allowing the body to reject the donor cells following the transplant. It also enables donor cells to travel via the bloodstream to the bone marrow, where they will begin to grow and generate new blood cells such as red blood cells, platelets, and white blood cells. Engraftment is the term for this procedure. (Leukemia and Lymphoma Society, 2021) When a transplant is successful, donor stem cells can take the place of bone marrow stem cells. It could also possibly be the patient's only hope for a long-term cure. One of the advantages of allogeneic stem cell transplantation is that the given cells form a new immune system when they engraft in the recipient's body. White blood cells are produced by the donor cells, fighting off any cancer cells left in the patient's body. This process is known as the "graft-versus-tumour effect," a process important as the conditioning treatment used to kill cancer cells. (Leukemia and Lymphoma Society, 2021)

#### *Graft-versus-host-disease*

In the case of an allogeneic transplant, the body may be susceptible to graft-versus-host disease (GVHD). (The Mayo Clinic, 2021) This develops when the new immune system's donor stem cells perceive the body's tissues and organs as foreign and attack them. (Graft-versus-host disease, 2021) "The recipient's immune system has mostly been destroyed by a conditioning treatment and cannot fight back, so the new stem cells make up most of the immune system after transplant." (American Cancer Society, 2021) GVHD can arise at any point following a transplant. The risk of GVHD is slightly higher if the stem cells originated from an unrelated donor, but it can happen to anyone who has a bone marrow transplant from a donor. (The Mayo Clinic, 2021) The chance of GVHD developing is "around 35% to 45% when the donor and recipient are related and 60% to 80% when the donor and recipient are not related." (Graft-versus-host disease, 2020) There are two types of GVHD: acute and chronic. Acute GVHD usually develops in the first few months after a donation, affecting the skin, digestive system, or liver. Chronic GVHD appears later in life and can affect many organs. Joint or muscle discomfort, shortness of breath, persistent cough are some symptoms of chronic GVHD. (The Mayo Clinic, 2019) Acute GVHD is characterized by inflammation, whereas chronic GVHD is characterized by autoimmune symptoms. (Rai V. et al, 2016)

#### *How graft-versus-host-disease affects the human organs*

A stem cell transplant can affect the body in different ways, both emotionally: depression, stress, and anxiety, and physically: fatigue, pain, hair loss, and infertility. To date, the heart has rarely been a target for GVHD, affecting mostly the mouth, joints, liver, eyes, gastrointestinal tract, and lungs. Several people with acute or chronic GVHD have developed bradycardia, coronary artery disease, or cardiac myolysis and have been reported. These symptoms ranged in severity from asymptomatic to deadly. Although

these cardiac symptoms are unusual, they are crucial to detect since they may indicate GVHD activity and may be reversible. (Rackley C. et al, 2005)

Chronic GVHD of the lungs develops when the donor's cells attack the tiny airways in the lungs. Lungs may become inflamed (red and swollen) and scarred as a result of this. Scarred lungs are no longer thin and lacey, instead, they are thick and stiff. (American Lung Association, 2016). The lungs stop working properly and shortness of breath is very common. It is likely that exercise or engaging in strenuous physical activity gets harder, resulting in coughing, chest tightness, or the inability to take a deep breath. With chronic GVHD there is an increased risk of lung infections. Early stages of chronic GVHD of the lungs are harder to detect, PFTs (pulmonary function tests) are the only tests that can find chronic GVHD of the lungs in earlier stages. (Fast Facts - GVHD of the Lungs, 2021) Infectious and non-infectious pulmonary problems affect 40 percent to 60 percent of all BMT recipients, resulting in significant morbidity and mortality. (Khurshid I. et al, 2002)

Another one of the major organs that are affected by graft-versus-host-disease is the liver. Chronic GVHD of the liver frequently manifests as "indolent cholestatic illness" in patients with skin, mouth, and eye involvement. Hepatic GVHD can be difficult to identify from other conditions such as infection and drug-induced liver injury in some circumstances. The combined effects of pretransplant chemotherapy, immunotherapy, GVHD prevention, and infection, commonly complicate clinical indications and symptoms. As a result, it's often critical to pay attention to and link clinical observations and laboratory data while making a diagnosis. (Karen E. et al, 2016)

## Methods

When reviewing data for this research analysis, a series of search engines were used to support the findings. These included PubMed, Postgraduate Medical Journal, Mayo Clinic, MedlinePlus Medical Encyclopedia, and the National Center for Biotechnology Information. To find more relevant information, keywords such as 'graft-vs-host-disease,' 'stem cells,' 'allogenic,' and 'organs' were used. When put through Pubmed, (n=669) related searches were found, of these searches (n=13) were screened and (n=6) were used in the final paper. The Postgraduate Medical Journal showed (n=14) results, (n=6) were further looked into and (n=1) was used. MedlinePlus Medical Encyclopedia gave (n=151) results, from here (n=25) were reviewed and (n=2) were used. The National Center for Biotechnology Information generated (n=1088,) (n=33) were reviewed and (n=6) were used in the final paper. Mayo Clinic showed (n=46) results, (n=6) were screened and (n=2) were used. Other than the five main search engines (PubMed, Postgraduate Medical Journal, Mayo Clinic, MedlinePlus Medical Encyclopedia, and the National Center for Biotechnology Information) other smaller independent sources were used. These were used to add clarification to the paper and have more detail. (n=8) sources were from independent sources such as sciencedirect.com, the European Respiratory Journal, cancer.org and more.

The sources that were used were focused on allogeneic transplants. Leaving the spectrum to include all types of stem cell transplant, allogeneic, autologous, and umbilical cord blood transplant, the searches were coming up broad and did not entail enough detail relating to the topic. Many of the studies that were screened were eliminated because of the sample size being too small — less than ten people— or because some of them were performed on animals, such as rats and mice. Since the focus was how graft-versus-host-disease affected human organs those sources were excluded.

Of the (n=83) sources that were screened, the ones excluded (n=23) were because of the date they were published (older than 20 years,) checking if there was a substantial amount of information and making sure there were solutions and discussions included. The sources that were screened and eliminated, were due to the fact that the information was generalized and wasn't giving specific information. Though one source from the Mayo Clinic was used even though the specificity of the type of stem cell transplant wasn't included. This source was included because it worked as a good base and provided key facts for the paper. Next, the (n=60) sources that were included in the second screening were all put into a spreadsheet and were skimmed to see the author's credibility, sources used, and relevance to the topic. The (n=26) that were used in the final search was determined by reading the abstract of the paper and/or the conclusion. Here several were eliminated again because they were either too broad or didn't provide the relevant information. Oftentimes, instead of talking about an allogenic transplant, they would discuss the effect of GVHD from an autologous transplant, or it would go into detail about how to help cope with it and not the chronic effects. The credibility of the author and publisher were also both taken into account during this process. In the spreadsheet, other than having just the title of the source and a citation, some jot notes were taken below it to have an easy visual of what information was on each website.

## Results

a study was performed at the Erciyes University Medical Faculty from May 2008 through June 2010. In this study, they looked at and studied the "Cardiac Effects of Chronic Graft-versus-Host Disease after Stem Cell Transplantation." This analysis included 40 patients who had received bone marrow transplantation: 14 with chronic GVHD and 26 without. Before bone marrow transplantation, all patients had baseline echocardiograms and were closely monitored.

Following the estimated time for GVHD after transplantation had passed — 100 days — these patients were split into two groups based on whether they developed chronic GVHD. It was found that chronic GVHD is linked to an increase in left ventricular mass and deterioration in left ventricular diastolic function in patients. In addition, it demonstrated that in these patients, inflammatory markers rose to higher levels. Inflammatory markers such as C-reactive protein (a protein made by the liver), erythrocyte sedimentation rate (type of blood test that measures how quickly red blood cells settle at the bottom of a test tube), and plasma viscosity (a measurement of the amount of protein in the blood's liquid portion) are frequently used in primary care to diagnose and monitor inflammatory illnesses such as infections, autoimmune diseases, and cancerous growth. (Dogan A. et al, 2013)

In 2014 a study was conducted by the European Respiratory Society looking at "Pulmonary graft-versus-host disease (GVHD) post stem cell transplant." Serial pulmonary function tests were performed on patients having stem cell transplantation for hematological malignancies, cancers that affected the blood, bone marrow, and lymph nodes. A high-resolution CT scan was used to investigate symptoms of increasing breathlessness or a decline in pulmonary function. Adjuvant chemotherapy was given to six patients, and complete body radiation was given to seven others. Breathlessness worsened in 10 of the participants. Within a year of their stem cell transplant, three people experienced pulmonary GVHD. (Jayaraman B. et al, 2012) Graft-versus-host disease was discovered to target the small airways in the lungs, causing them to become inflamed, red, and swollen, scarring them. (Fast Facts - GVHD of the Lungs, 2021)

In 2000, a study was conducted looking at the liver condition of 130 patients before and after bone marrow transplants at the Catholic

Hematopoietic Stem Cell Transplantation Center. Liver dysfunction occurred in 85 of the 130 patients. GVHD and medication hepatotoxicity were the leading causes of allogeneic bone marrow transplant failure. Before the transplant, 18 out of 130 patients, 13.8%, had abnormal liver function tests. These patients showed no higher risk of post-transplant liver dysfunction, GVHD, or death as compared to patients who had normal liver function tests prior to their transplant. (Kim B. et al, 2000) Hepatic graft-versus-host disease is a common complication following bone marrow transplantation that commonly leads to death. When dealing with this type of scenario, a liver biopsy is necessary to confirm the diagnosis in patients of liver impairment that developed within 100 days of transplantation. To avoid chronic GVHD in patients with acute hepatic GVHD, substantial immunosuppression is required. (Chiba T. et al, 2005)

### **Conclusions and Discussions**

The goal of this systematic review was to assess the effects of graft versus host disease on the three main human organs. The effect GVHD had on the heart, lungs, and liver after an allogeneic stem cell transplant were evaluated through (n=26) sources. Cardiac effects of GVHD are seen to be rare as compared to the effects of it on an organ like the lungs, but after the study in 2010 by the Erciyes University Medical Faculty, it has been proved crucial to detect since they may indicate irreversible effects. When fourteen out of forty people developed chronic GVHD, long-lasting effects were shown in the heart. (Dogan A. et al, 2013) Left ventricular mass was increased, which oftentimes is an indicator of death and heart failure caused by coronary artery disease. (Greater left ventricular mass increases the risk of heart failure, 2019) Diastolic function was damaged in the left ventricle which has been linked to mortality, heart failure, and hospitalization. (Sherif F. et al, 2020) As well as inflammatory markers rising post GVHD in the heart and it can cause a number of things, ranging

from infection to cancer. High C- reactive protein was also found and signals inflammation in the heart's arteries which may lead to an increased risk of a heart attack. Through these three main effects on the heart, it can be seen that even though it may be uncommon for there to be cardiac effects, it is important to monitor any changes that occur in the body, which may lead to something much more full scale and fatal.

When looking at the respiratory effects of GVHD, a study conducted in 2014 by the European Respiratory Society, it was seen that small airways were targeted, inflaming them and making them red and swollen. Breathlessness worsened and rigorous physical activity was also harder than usual for most. Small tasks like breathing may be subconscious but are one of the most important functions of the body. (Jayaraman B. et al, 2012) Having identified the effects of GVHD on the lungs can change a patient's lifestyle and could make the most significant difference.

Hepatic effects of GVHD were shown as high serum aminotransferase levels ("the most common causes of elevated transaminase levels are nonalcoholic fatty liver disease and alcoholic liver disease.") (Oh R. et al, 2017) reflecting severe viral hepatitis. Tests revealed damaged and degenerative small bile ducts, typical with GVHD. (Strasser S. et al, 2000) The liver being a very important organ of the body, identifying the effects it has on the liver after an allogeneic transplant is vital to the patients' health. It was shown that with progressive cholestatic symptoms there was evidence towards loss of tiny bile ducts and portal fibrosis in situations where the diagnosis was not made and therapy was delayed. (Strasser S. et al, 2000)

After assessing all the potential risks of getting an allogeneic stem cell transplant the question comes up of whether or not the transplant is more or less favourable. Looking through the data and findings, an autologous transplant looks like a

much better option. If an individual isn't getting donor stem cells, then the risk of getting GVHD wouldn't even be present. Keep in mind however that everything has a positive and negative side. In the scenario that an individual is getting an autologous transplant, there isn't the risk of GVHD but there is still the chance that the problem is reduced but not eliminated or for it to work as a combination of therapies. Looking on the opposite side, in an allogeneic transplant even though there is the risk of GVHD there is still the complete replacement of host cells with donor cells and elimination of reservoirs for the disease. Whether or not to get an allogeneic transplant would differ from person to person. The best way to see which type of transplant would work best, it would be essential to look at what is important to the individual and take into account their unique scenario. Oftentimes, allogeneic transplants are preferable for those who are at risk of relapse and who can take medication to prevent GVHD. While an autologous transplant might be a better option if the body is producing enough healthy bone marrow cells for the transplant to be successful. The future of medicine is very bright, by just looking at the past hundred years there have been countless discoveries in medicine, hepatitis C treatment, updated cystic fibrosis treatment, 'smart' defibrillators, and more. The transplant of organs and how the rest of the body reacts is an important topic that warrants more research. In the future, I think it would be important to see if GVHD is somehow avoidable. The current strategies for preventing acute GVHD are very effective. Chronic GVHD, on the other hand, is less understood and more difficult to prevent. Could we possibly re-code our immune system to not see donor cells as a threat without compromising the immunologic benefits? This would need to be heavily considered and looked more into with regards to how it could affect people in the long term, — genetic mutations can lead to many disorders and illnesses so that would have to be taken into consideration — and with discussions of ethical problems. In regards to

ethics, there are many points to look at, safety, justice and equity where it can be argued that it will only be accessible to the wealthy, and religious objections. The importance of this topic can be seen through this paper, further proving that additional research will greatly benefit the field of regenerative medicine and make it will be very worthwhile in the future.

### *Limitations*

While writing this research paper the focus was the effect of graft-versus-host-disease on the three main organs, focusing on three organs limited the reader from getting an in-depth view of the effects. While I was looking at the general effect of the disease alternatively by looking at just one specific organ there would have been more information about the signs and symptoms, effects, and how it changes someone's lifestyle. Larger sample size could have also been evaluated. Having more people as well as age, race, gender, would have helped in getting a broader view and a more accurate conclusion. There were also a limited number of sources that were accessible, many had a subscription fee or required identification. Having these financial resources and extra aid also would have helped in broadening the search and getting more accurate and in-depth results.

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# The Effects of Digital Media Use on Youth Brain Development – A Systematic Review

Stefan Iordache  
University of Alberta, Canada  
iordache@ualberta.ca

## Abstract

**Background:** Excessive technology use in youth has been related to poor brain development. This literature study looks at the connection between digital media use and brain development in children and teenagers. **Methods:** Medical journals were analyzed in order to gather data for a systematic review. PUBMED and JSTOR were utilized to perform the searches. The abstracts and titles of the papers were inspected first, followed by the remainder of the paper. Full texts were examined and processed, and information was retrieved for use in the study. **Results:** Overall, the published data showed a strong link between digital media use in youth and poor white-matter tract integrity, especially in the Broca (speech production) and Wernicke (language development) areas of the brain (Korte, 2020). The white matter tract integrity of the brain is a universal trait, and the difference in integrity can help explain the mind's processing speed. Contrastingly, technology cannot be labeled as only having negative effects. With moderate use and consideration, digital media can be a way to expand one's knowledge. There are many opportunities to learn and grow with technology if the correct mindset is established. For now, there is not one set answer on the effects of digital media use. Extensive use will negatively impact youth health and brain development, nevertheless, benefits arise with moderate use. When more studies will become available, providing measurable accurate data on digital media utilization, progress can be made in

ascertaining how to reap the benefits of the digital informative technology.

*Keywords: Technology, Brain Development, Digital Media*

## Introduction

Technology makes up a major piece of society and it is becoming ever more prevalent. The word "technology" used in this systematic review refers to "information technology" defined as the use of hardware, software, services, and supporting infrastructure to manage and deliver information using voice, data, and video (Michie, 2020). The true degree of the impact that technology has on people and our brain development is perplex (Anonymous, 2018). Technology has taken a strong hold on our lives, especially in the younger generation. Children are likely to invest more time on the internet and less time interacting with other people, face to face. However, functional imaging scans show that internet naive adults who figure out how to utilize the web, show significant increases in brain neural activity during online searches (Small et al., 2020). Certain computer projects and video games might improve memory, multitasking abilities, fluid intelligence, and other cognitive capacities (Anderson and Subrahmanyam 2017). There is not one conclusive standpoint that explains of the technology's effect on brain development. In moderation, the utilization of technology can be useful and allow for more parts of the brain to be used (Giedd, 2020). The risk for reward concept relates to social media platforms that directly

affect the brain reward centre and indirectly lead to addiction, anxiety and depression (Anonymous, 2021). On one hand, social media as a mean of technology use adds up to the amount of time adolescents spend online. On the other hand, it influences well-being and opinion formation. (Crone et al., 2018). Socializing on media engines could cause the brain to change and grow. Time spent learning or experiencing something is encoded in the brain by subtle changes in the strength of connections between neurons. (East, 2016). Similarly, to an appropriate work - life balance, technology use to social interactions equitable ratio is as important. The objective of this literature study was to analyze available literature, dealing with the potential effects of technology on youth brain development, with emphasis on the purpose and time scale of digital media use as indicators of impact on brain betterment.

## Methods

A systematic review of research papers was conducted in order to gather data from multiple viewpoints. All studied papers were written in English and searches were done through PUBMED and JSTOR. Papers were generally screened at first, with the titles being reviewed, followed by further analysis. To allow for replicability, key words were used to conduct these scans. This formed a collection of possible papers to analyze. The terms included in the search were: “brain”, “technology”, “development”, “digital media” and “neuro”. By narrowing it down to these terms, irrelevant papers were less likely to appear, and search results had a greater chance of aligning with the selected systematic review topic. In total, 109 papers were produced by the original title scan. Once reviewed, papers with relevant titles were used for abstract analysis. From there, abstracts of 14 papers were looked at. Many of the papers in the original selection were removed from further analysis due to irrelevance. Some articles mentioned ideas about digital media use but did

not relate it to the brain in any way, while other papers would discuss brain development of those with diseases.

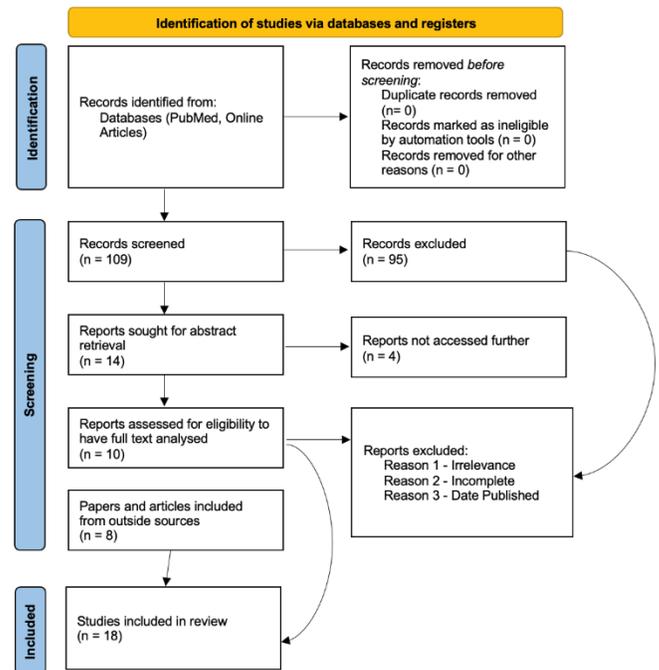


Figure 1: Schematic illustration of the evaluation procedure used for the systematic literature review

Furthermore, there were several articles which appeared to be relevant but could not be accessed with the available means (i.e., paid subscriptions, incomplete documents). The final criteria for exclusion involved assessing the date of publication. Only articles which were published from 2015 to present were considered to have reliable data. Essentially, in order to align with the proper requirements, abstracts needed to be published recently in terms of scientific research, and mention ideas about the effect of digital media on the brain. If the abstract was on this general topic, full texts were analyzed, and data then extracted to be used in the research. Of the 14 abstracts which were read, 10 papers were then examined and analyzed in detail. Several abstracts which were read were not included as the paper addressed a different topic than the one

of current interest; not enough data could be obtained for relevant research purposes. With the remaining papers, the data obtained were interpreted and used in a review. In addition, there were 8 other papers and articles included, which were obtained from outside sources. These reports had relevant information which could be directly applied in the study. A total of 18 papers were used to gather data for this systematic literature review.

A PRISMA 2009 diagram was applied as an evaluation procedure to guide and route the source information (Moher et al., 2009) – Figure 1.

## Results

People who are constantly using technology have less opportunity to communicate offline and rest their brain in its default mode (Small et al., 2020). Neurological ramifications have been associated with internet addictions. There is a significant connection between early childhood digital media use and poor white-matter tract integrity, particularly between the Broca and Wernicke brain regions. Although it is not certain if social media or the act of looking at screens is the cause of poor sleep, it has been proved that exposure to certain wavelengths of light dictates the circadian rhythm that influences sleep. Most light emitting diodes (LEDs) from computers and phones give off a slow wave of blue light that negatively impacts the circadian rhythm (Small et al., 2020). The utilization of technology impacts the brain, forming different connections and changing human cognition. An environment that encourages short attention span, without interpersonal communication, and that is addictive or compulsive will shape a person's life. Digital media can leave an unprecedented mark on the brain, especially since some teens are racking up to nine hours of digital media use a day (Briggs, 2017). In limited application this use might not have negative effects, but studies show that time spent online is increasing. In 2005, adolescents spent about eight hours per week

online, while in 2017 the average had more than doubled to 18.9 hours a week (Przybylski and Weinstein, 2017). The degree to which this extensive use of digital media is viewed as harmful or beneficial all relies upon how it is being utilized and for how long.

Technology has been shown to have its benefits. In moderation and with good intentions, technology allows for our brains to develop new skills and increase cognitive performance. A group of scientists led a study which looked at brain neural activation in cognitively normal adults. One group had minimal internet search experience, labeled the net naïve group. The other set of people had extensive experience and were referred to as the net savvy group (Small et al., 2020). Both groups were subject to internet learning and stimulating activities. MRI scans were taken before and after. The net-naive group's scans showed that more parts of the brain were used and developed after being subject to the novel internet activities. The results of the net-savvy group were even better however as in the internet search task, this group displayed a more than twofold increase in the extent of activation in the major regional clusters compared with the net-naive group. The results imply that internet searching is a form of brain exercise. This suggests that even after continued use, digital media can still remain novel and offer a mentally stimulating experience (Small et al., 2020).

Brain scans can be examined to study attention and focus capacity in humans. A study that used neuroimaging developed scans of frequent and irregular internet users. In those people who routinely used the internet, the prefrontal cortex of the brain was twice as active compared to irregular internet users. This prefrontal cortex part of the brain is used for rapid decision making and short-term memory. Essentially, when there is a stream of information, we have developed the ability to skim, showing that technology in a way has allowed for our brain to develop new skills (Horvath, 2015).

This idea that using technology can enhance the brain's capacities is an extrapolation from the displacement hypothesis. In moderation, digital media can help develop the brain. However, the hypothesis implies that the harm of technology comes from extensive exposure and is directly proportional to the use. Many of the negative effects attributed to technology use arise since people will forgo activities and interacting with others to instead spend more time on digital media (Przybylski and Weinstein, 2017).

In order to identify if youth are overusing digital media and therefore harming their brain development, an analysis of several regression models tested how engagement with digital screens was related to mental well-being, assessed with the Warwick-Edinburgh Mental Well-Being Scale. This is a 14-item self-report instrument validated for use in general population samples of individuals ages over 12 years that can measure the life satisfaction, psychological functioning, and social functioning of participants (Przybylski and Weinstein, 2017). The regression models showed an increase in mental wellbeing with technology use, rising until a peak at about two hours of use a day. Further engagement produced a negative correlation between daily digital screen involvement and mental well-being, often drastically decreasing around the 5-hour mark (Przybylski and Weinstein, 2017). Mental well-being is necessary for healthy brain development, so these models go to show how both limited and extensive technological use can inhibit proper cognitive growth.

## Discussion

There is a limit as to the level of certainty researchers can ascertain technology as having a positive or negative effect. The vast majority of current neuroscientific research on digital media use relies completely upon self-reported characteristics. Although multiple testing factors can be introduced, i.e., the Warwick-Edinburgh Mental Well-Being Scale, people may not be reporting their data truthfully, which skews

results. To combat this issue, neuroscientists should aim to incorporate larger datasets and use more refined methods to account for what happens on screens, for how long, and at what age. However, this raises questions of ethical measures and whether it is allowed for people to be tracked to this extent, even with permission. Nonetheless, if these changes can be implemented, assertions made about technology use on brain development will have greater degrees of confidence.

In society today, technology can be beneficial. It allows for tasks to be accomplished with efficiency and flexibility. People can learn new skills and expand their knowledge. However, the misuse and overuse of technology causes problems. Although some people use technology in moderation, the reality is that the majority of users are abusing the time spent on the task at hand. In a study in 2018 from the University of Pennsylvania, participants were split into two groups. The first was set the task of limiting their social media use to moderate amounts, about 10 minutes per app; not cutting it out completely, but just enough to be informed and move on. The second group was told to continue using social media to the extent they normally do. The results showed that the limited group had significant reductions in loneliness and depression during the study compared to the other set of participants (Anonymous, 2021). This reduction in negative feelings allows for the brain to function normally and develop properly.

With more time in front of a screen, people are neglecting interactions with other humans, one on one. There is a limit of what one can learn from a screen. After a certain extent, real human connections are required in order to grow. Younger populations are extremely at risk as their brains are in the prime stage of development (Hutton et al., 2020). The extreme influence of technology will cause gaps in their knowledge and in other areas of life. Although youth are more susceptible to the problem, adults are not excluded from this risk. By growing up in front of

screens, the youth brain is developing, but instead of making connections with other people and being put to good use, the time that could have been spent with peers, is instead used to interact with a screen. Developing brains are particularly vulnerable to this, and when exposed to high volumes of technology, the mind may adapt to frequent visual stimulation and have little need for change (Anonymous, 2018). When many hours are spent playing games or browsing social media, some learning does take place, but after a while the brain is mindlessly reacting, and has reached a plateau in terms of growth. Any excess use with mindless actions will not be beneficial (Odgers and Jensen, 2020). These people will have certain skills with technology, but when it comes to being a member of society, they lack the necessary ability to contribute meaningfully. Although this might be an extreme case, it is becoming more prevalent in our world.

Technology is making up a larger part of our lives every day. Kids are growing up with screens in their hands. However, technological use cannot be labeled as simply good or bad (Hogenboom, 2020). The research accumulated goes to show that there are benefits and drawbacks to technology use. It is a myth that all use of digital media is bad and harms our brains. In the way it is being used today, technology is often being misused which leads to the misconception. For children in preschool, watching television has been found to have both negative and positive effects. Research suggests that educational television has a significant positive impact on cognitive development (Anderson and Subrahmanyam, 2017). Insufficient technology use can deprive younger people of digital interactions with peers and limit important social information that can be obtained. Overuse can displace time which could be used for meaningful activities (Przybylski and Weinstein, 2017). If one takes a step back, it can be realized how useful and beneficial technology is. We have dictionaries, quizzes, educational software, eBooks, games to expand cognitive

growth, apps that can improve working memory and many other tools right at our fingertips (Resnick, 2018). "The dose makes the poison; it appears that both low and excessive use are related to decreased well-being, whereas moderate use is related to increased well-being" (Dienlin and Johannes, 2020). Digital media use is beneficial but has its drawbacks when overused (Korte, 2020). The next step is to clearly identify the benefits of technology and attempt to expand on them, while trying to inhibit the drawbacks of digital media.

## Conclusion

Multiple research studies have revealed that technology overexposure is affecting our brain health and it may be necessary to include restrictions, such as a change in the school code or implementation of laws to limit technology use to moderate amounts. With limitations on the extent of technology one can use, the brain can develop rightly and form connections with peers, a necessary part of growing up.

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# FreeFeed: Combating Degenerate Feedback Loops With Linguistic Inferences From Human Interactions On Social Media

Aashika Jagadeesh

Fair Lawn High School, United States of America

aashika.jagadeesh@gmail.com

## Abstract

Social network recommendation systems are frequently linked to encouraging polarization and widening ideological division, but this effect has rarely been examined in detail. Pernicious feedback loops are often created when these systems are trained with data that originates from users already exposed to algorithmic recommendations. This study analyzes the influence that feedback loops have on user mental health and assesses the effect of a Bayesian choice model (FreeFeed) in its ability to prevent the harmful reinforcement of views. At first, the Twitter API was filtered off of 4 factors: drugs, relationships, academics, and physical appearance. After 120,000 tweets were collected and preprocessed, the tweets were used to train/test a generalized logistic regression model and a multi-layer perceptron neural network. The models were compared on values such as the F1 score (max 0.963), AUC(max 0.990), and accuracy (max 93.7%). The algorithm was then implemented into an online simulation and tested on a set of social media users ( $n = 102$ ) in New Jersey to identify both the impact of the revised model and the recommendation system model on self-esteem. Over the course of 3 weeks, participants completed a survey before and after use, in which responses were scored on the Rosenberg Self-esteem Scale. Significant statistical difference was determined between the

revised model and the recommendation system model in the online simulations, which proves that policy makers and platform users should take these effects into consideration when they govern the use of feed algorithms.

*Keywords: Machine Learning, Polarization, Human-Computer Interaction, Social Behavioral Science, Ethical AI*

## Introduction

Echo chambers and degenerate feedback loops function as metaphors that encapsulate the public fear that recommendation systems can manipulate user opinion by limiting the information users can consume online (Jiang et al., 2019). A primary concern is that recommendation systems combine with the tendency to communicate with like-minded individuals to create an environment that primarily presents opinion-reinforcing content to users. Recently, advances have been made in understanding the direct influence that recommendation systems have on the dissemination of fake news. According to Cohen (2018), users may believe misinformation as a result of algorithms that tailor cultural artifacts customized to the user in the form of a social distribution system. It was also noted how these algorithms sophisticate an understanding of social network analysis through their "invisibility" in the public eye. In this sense, users often fail to

understand how fake news integrates its way into the user feed. Further work was done on researching the correlation between echo chambers and political homophily, where researchers suggested that homophily was more apparent in the network of reciprocated followers than in the nonreciprocated network (Colleoni et al., 2014). In addition, studies conducted by the European Union Institute for Security Studies (EUISS) have demonstrated the relationship between echo chambers in social networks and the spread of vaccine misinformation online (Raemdonck, 2020).

Along with political bias and the spread of misinformation, various bodies of work have attributed mental health disorders to the extensive use of social media networks. For instance, in the Department of Psychology in Toronto (Hogue et al., 2018), 118 female undergraduate students were tasked with liking an image of an attractive peer and completing a visual analogue scale measure of state body image. It was concluded that young women who interacted with posts of an attractive peer experienced an increase in negative body image shortly afterwards. Further work done by researchers at the University of Cologne (Appel et al., 2015) helped establish a relationship between Facebook use, social comparison, envy, and depression. It was found that social comparisons and envy were common experiences amongst users on social media apps.

Although the notion of echo chambers is well-accepted, its direct influence on mental health and user consumption is not often well-understood. We seek to characterize the influence of feedback loops in the context of the recommendation system and study the consequences of algorithmic confounding on user self-worth. As these systems have been linked to altering user opinions and decisions, it is well within our ethical responsibilities to understand the system's implications for individual health and self-esteem. Issues of fairness and transparency

in the creation of suggestion softwares must be considered. It is our hope that researchers will use our work to assess the impact of recommendation systems across all users and develop efficient models with reduced degeneracy.

The main contributions in this paper are as follows:

- This study proposes FreeFeed, a Bayesian *choice model*, which accounts for opinion-reinforcement and limited exposure to alternative views. The model is fair by preventing negative bias towards unrepresented alternatives. In this sense, marginal probabilities of selecting specific options that were never presented to the user are independent of other choices.
- A simulation of FreeFeed was created by collecting 120,000 tweets from the Twitter API and training an NLP algorithm. A generalized logistic regression and a multi-layer perceptron were tried. The NLP algorithm was then implemented into an interactive website, along with a control algorithm that recreated the effects of feedback loops in recommendation systems.
- The website was tested on a set of social media users (n=102) from ages 15 to 25. Participants were split into three cohorts: a control exposed to an algorithm that resembled the effects of a traditional recommendation system, a group that used FreeFeed for 15 min per day, and a group that used FreeFeed for 30 minutes per day. The psychological study was conducted over the course of 3 weeks, and participant progress was regularly monitored.

### **Description of Choice Model**

A discrete choice model determines the probability of a user selecting an option among K alternatives. It follows from the belief that utility of choice is a function of the properties of the choices and the characteristics of the individual

making the choice (Columbia Public Health, n. d. b.). In a given scenario, we can suppose that  $K$  is large, but users are limited in the options they can choose from. Sets of choices are made from selected subsets of alternatives, where  $C$  is an indication of all non-empty subsets of  $K$  (Train, 2002). In this study, we examine the probability of selecting an item  $K$  from a presentation  $C$ . Our proposed model, FreeFeed, conforms to the independence of irrelevant views. That is, sets of choices  $\{K_t\}_{t=1}^T$  are subject to chance variation and the probability of selecting a specific option is independent of other items in a given presentation  $\{C_t\}_{t=1}^T$ .

This type of decision making problem is often regarded as a bandit problem (Lattimore et al., 2019). With a bandit framework, the Bayesian model serves two primary purposes: observations are used to better inform inferences of user preference and posterior samples induce effective presentation mechanisms, where the current best alternatives are explored. The posterior frames  $k$  with high priority either when  $k$  was rarely presented or frequently selected. This thus follows Thompson Sampling (Thompson, 1993), ensuring that underrepresented options will appear later on. For instance, in a subset  $\{3,4\}$ , if 3 does not appear in a single iteration, it is guaranteed a second presentation with Thompson Sampling.

#### Data Collection for Choice Model Simulation:

Both ground truth and test data were collected through the Twitter API (Twitter API, 2012). To communicate with the Twitter API and collect real time tweets, the Tweepy Python library (Tweepy Twitter API, 2020) was used. A python script was created with the Tweepy Twitter API and ran over the course of a month. Data was filtered on parameters that prevented the collection of retweets, tweets from automated accounts, companies, etc. Tweets were also filtered off of 4 factors: relationships, academics, drugs, and physical appearance (Table 1). Training data was

High-Stress Factor	Presence in Tweet
Relationships	<p><b>Viewpoint #1:</b> tweets mention girlfriend, boyfriend, family, friends, parties, etc.</p> <p><b>Viewpoint #2:</b> tweets mention being single, alone, or independent</p>
Academics	<p><b>Viewpoint #1:</b> tweets mention college applications, assessments, GPA, professors, teachers, clubs, sports</p> <p><b>Viewpoint #2:</b> tweets promoting calmness, meditation, self-confidence</p>
Drugs	<p><b>Viewpoint #1:</b> tweets mention being drunk, commercializing excessive drug use, informal references of drugs</p> <p><b>Viewpoint #2:</b> tweets mentioning downsides of excessive drug uses, discouraging substance abuse, providing support for drug addicts</p>
Body Image/Physical Appearance	<p><b>Viewpoint #1:</b> tweets promoting weight loss, dieting, commercializing cosmetics and weight loss products, promoting modeling agencies, etc.</p> <p><b>Viewpoint #2:</b> tweets promoting body positivity, natural beauty, etc.</p>

filtered in this fashion to focus model function on identifying the relationship between degeneracy and user mental health.

TABLE 1: Tweet Filtering Criterion

However, to truly simulate the nature of the Bayesian choice model, the model was trained to distinguish between alternate perspectives. Tweets were then classified into high-stress factors and viewpoints (if applicable), yielding a dataset of ~800,00 tweets. Furthermore, a second round of validation was completed to remove misclassified and irrelevant content, which resulted in a dataset of ~120,000 tweets. Factors and perspectives were kept primarily balanced.

After data was collected and fully filtered, preprocessing was conducted. Unicode characters and stop words (ex. the, or, and) were removed and replaced with an empty string to ensure that there was no impact on model training. Lemmatization was then performed on the dataset to reduce words in the tweets to their basal/dictionary form. The Stemming technique

was also used to reduce words to their word stem by inflection.

After the training matrix was fully formatted, a Generalized Logistic Regression Model from the Scikit learn library was used to develop the first model (Scikit Learn, 2020). A Multilayer Perceptron Model (neural-network based approach) was then tried. Next, the models were created and scored on the data from a test matrix.

### Website Design Implementation:

The trained models were implemented into a website created from Angular and a Node.js backend (Figure 1). The site was made to resemble the appearance of a user feed, with the option to view, like, and reload posts. A user's interaction history was stored in the Firebase API and used to determine which posts would appear next. In this way, each user's feed was unique to a user's individual preferences. Unlabeled tweet and image sets were created as a post bank, which could be retrieved from when the user pressed reload. All tweets and associated image sets were collected from Twitter Streaming API and filtered off of relevance to a factor in the filtering criterion (Table 1).

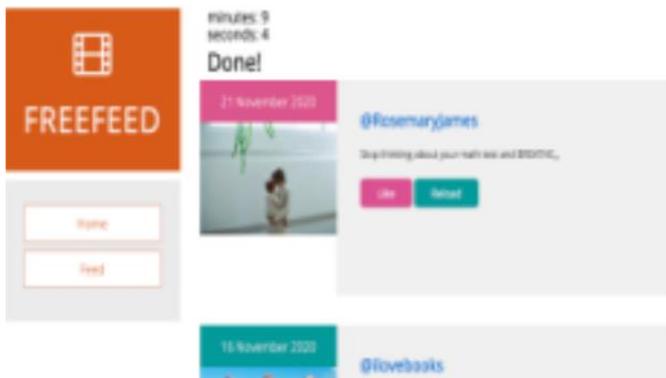


FIGURE 1: Website for model simulation

The unlabeled datasets served as input, in which the model classified the factor and viewpoint that was promoted. To be properly classified as demonstrating a specific factor or viewpoint, the model would need to pass a minimum confidence threshold of 0.65.

If the score passed the minimum threshold, the post would be labeled and used to determine which posts to present after reload is pressed. When the user interacts with labeled post, the post and its corresponding classification are stored in the Firebase API. Depending on the frequency of user interactions with identically labeled posts, the model would begin to alter the feed and introduce posts demonstrating alternate viewpoints.

### Psychological Study:

Social networks were used to recruit participants, as this would ensure that all test subjects were social media users. The sample was constituted of random social media users in Fair Lawn, New Jersey. Parental approval was required for test subjects that were less than 18 years of age.

A self-esteem survey was provided to each of the participants prior to using the website, which entailed a total of 10 questions (shown in the Appendix). The questions included statements such as "I certainly feel useless at times" and "I take a positive attitude towards myself." Participants responded with how much they agreed with each of the statements by bubbling in the following: Strongly Agree, Agree, Disagree, Strongly Disagree. The responses were scored on the Rosenberg Self-esteem Scale of 30 points (Center of Disease Control, 2005). Each choice was worth a certain number of points from a scale of 0 to 3. After completing all 10 questions, a participant could have a minimum score of zero and a maximum of thirty. Scores between 15 and 25 are considered to be average, while a score exceeding 25 suggests an extremely high self-esteem; a score below 15 suggests an extremely low self-esteem (SRLab, 2014).

Participants were randomly assigned to 3 cohorts: a control that used a feed that resembled the effects of a traditional recommendation system for 15 minutes per day (Group 1), a group

that used FreeFeed for 15 minutes per day (Group 2), and a group that used FreeFeed for 30 minutes per day (Group 3). Group 1 had 35 participants, Group 2 had 34 participants, while Group 3 had 33 participants. With these divisions, the cohorts were kept primarily balanced. The website had two settings: a sample feed with an algorithm that mimics the function of recommendation systems and a sample feed that deploys the FreeFeed algorithm.

Results were primarily based off of self-esteem scores, which were compared before and after use to determine the direct effect of the choice model. Score differences were then averaged across the span of three weeks to serve as viable data points. Demographic data was also analyzed to determine basic characteristics of the sample population. Model accuracies were computed to determine how effectively the models simulated a particular choice model. Furthermore,  $\chi^2$  tests were conducted to identify stochastic variables when users interacted with the feedback loop. All analyses were performed at a significance level of 5%, and tests were two-sided. The 95% confidence intervals (CI) of odds ratios (OR) were calculated as well.

## Results

### Demographics

105 participants initially were collected in total, with respondents consisting of males (n = 43) and females (n = 62). Three participants did not use the application for a long enough period of time before reporting their self-esteem score or fully interact with the FreeFeed interface for 3 weeks. Only 102 respondents were considered in the final data to reduce error and bias rates.

The breakdown of ethnicities was as follows: 42% of participants identified as Asian; 42% identified as Caucasian; 9% as African-American; 12% as Hispanic/Latin-American. All subjects were between ages 15 and 25.

### Self-Esteem Scores:

Male self-esteem scores averaged to be greater than that of females [19.08 vs. 16.75;  $t = 1.720$ ;  $p = 0.086$ ] (Table 2). The average score difference for participants in Group 2 was 3.89, while the average score difference for Group 3 was 4.69. Group 1, on the other hand, exhibited results that varied significantly from Group 2 and 3 with a score difference of -2.24 (Figure 2). Both the Bayesian choice model [ $t = 2.027$ ;  $p = 0.025$ ] and the simulated recommendation system [ $t = 2.331$ ;  $p = 0.012$ ] instigated significant changes in user self-esteem (Table 3). There were a few outliers in the data, where participants exhibited no change in scores after extensive use. Some participants experienced changes that allowed for a 10-point increase, which resulted in significant fluctuations. In this sense, model training was not inclusive enough to have an equal impact on all

Mean Score	18.64
Male Mean Self-Esteem Score	19.08
Female Mean Self-Esteem Score	16.75
Range	25*
Median	17

\*5-30

individuals involved in the study.

TABLE 2: Participants from all cohorts

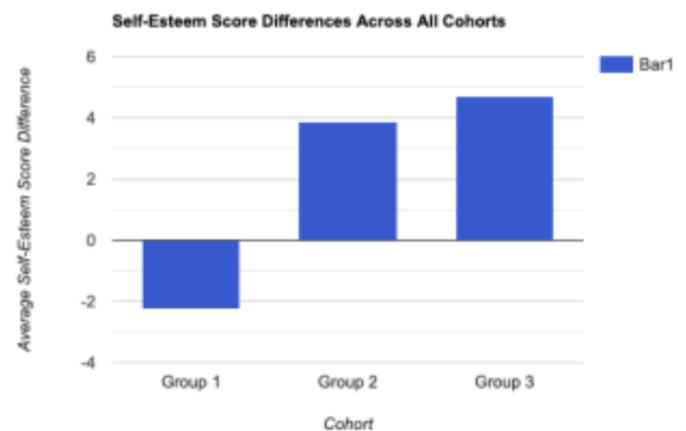


FIGURE 2

Users from group 3 exhibited more magnified increases in self-esteem scores, which indicates a positive relationship between the time spent

interacting with the choice model simulation self-esteem. By the contrary, the relationship depicted by the control cohort follows a different trend: there was an average decline in self-esteem scores (Table 3).

Effect of Bayesian Choice Model (15 min) & Simulated Recommendation System (15 min) on User Self-Esteem					
	$\alpha$	$\sigma$	Mean difference	t-statistic	p
Bayesian Choice Model (FreeFeed)	0.05	7.182	3.89	2.027	0.025
Recommendation System	0.05	2.321	-2.24	2.331	0.012*

\* $p < 0.05$

TABLE 3

A negative relationship can thus be seen between the usage of the recommendation system and the self-esteem scores of individuals.

One of the primary purposes of this was investigation was to determine if a discrete Bayesian choice model could have a significant influence on self-worth when compared to traditional recommendation systems. The results of univariate logistics demonstrate that there is significant statistical difference between both the choice model and recommendation system simulation in their effect on self-esteem [OR = 2.03; 95% CI OR = 1.48–2.82,  $p < 0.05$ ] (Table 4).

Statistical Difference Between Bayesian Choice Model and Simulated Recommendation System	
	Value
$\alpha$	0.05
$\sigma$	0.896
z	1.65
$\bar{x}$	1.479

TABLE 4

### Model Performance:

After models were fully trained, metrics were collected and analyzed. Some discussions follow. Loss was measured through Sparse Categorical Cross Entropy, and the loss was minimized after 200 epochs. The loss value of the Multi-Layer Perceptron Neural Network was 0.183, while the loss value of the Logistic Regression Model was 0.223. Using the formatted test matrix, the final accuracy of the Neural Network was calculated to be 93.7%, and the final accuracy of the Logistic Regression model was 88% (Figure 3).

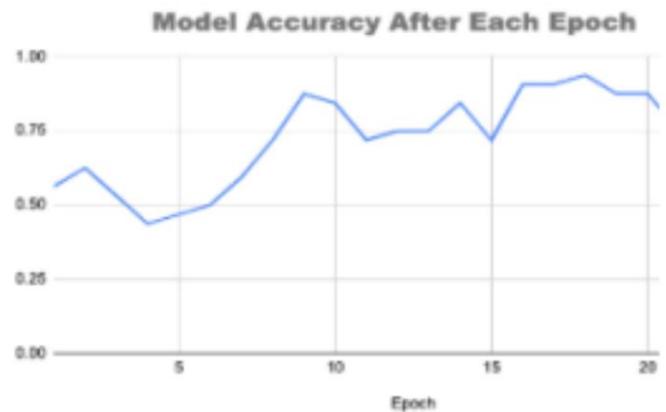


FIGURE 3: Model accuracy growth curve for the Logistic Regression Model for every 20 epochs

### Logistic Regression Vs. Multilayer Perceptron

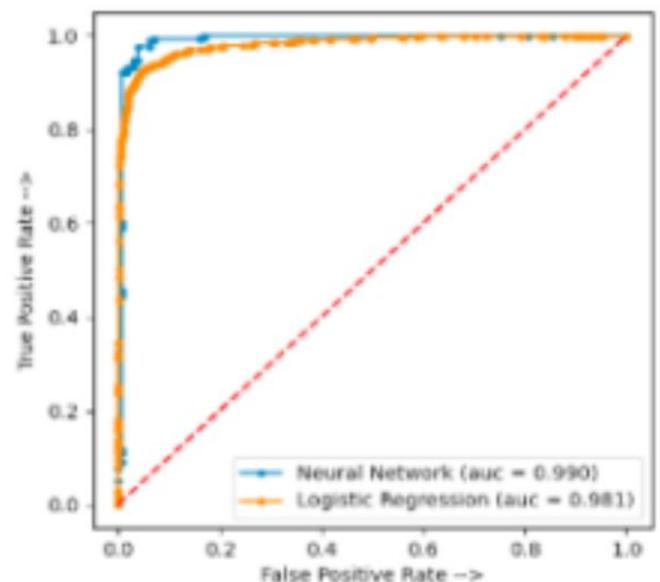


FIGURE 4

As an example, Figure 4 compares the ROC curves of the Neural Network and Regression Model. The curves are above the random decision line, which exists at, i.e., the (0,0) to (1,1) diagonal, thus indicating that they are good decision tests. Even at a True Positive Rate of 70%, almost all False Positives can be eliminated for both models. In this sense, the models are capable of making a rather accurate decision about classifications regarding linguistic structure. The AUC (area under the curve) was also measured, and the Multi-Layer Perceptron ultimately achieved the maximum AUC of 0.990. Taking into account the false and true positive rate, the F1-score was calculated. It was calculated separately for both views (Table 1), the macro average, and the weighted average (Table 5 & 6).

<b>Logistic Regression</b>	<b>Precision</b>	<b>Recall</b>	<b>F1</b>	<b>Support</b>
<b>Viewpoint #1</b>	0.89	0.93	0.91	998
<b>Viewpoint #2</b>	0.97	0.95	0.96	1,162
<b>Macro Average</b>	0.93	0.94	0.93	2160
<b>Weighted Average</b>	0.95	0.94	0.95	2160

TABLE 5: The Logistic Regression Model's Precision, Recall, F1-Score, and Support values are provided above. Viewpoints #1 and #2 refer to the classifications provided by Table 1.

TABLE 6: The Multi-Layer Perceptron Model's Precision, Recall, F1-Score, and Support values are provided above. Viewpoints #1 and #2 refer to the classifications provided by Table 1.

A Wilcoxon signed rank test (non-parametric) was used to quantify observed data and identify behavior that would result in significant statistical difference between the two models. Using the accuracy values, it was ultimately determined that there was significant statistical difference

<b>Multilayer Perceptron</b>	<b>Precision</b>	<b>Recall</b>	<b>F1</b>	<b>Support</b>
<b>Viewpoint #1</b>	0.96	0.93	0.94	998
<b>Viewpoint #2</b>	0.97	0.98	0.98	1,162
<b>Macro Average</b>	0.97	0.96	0.96	2160
<b>Weighted Average</b>	0.97	0.97	0.97	2160

between the Logistic Regression Model and Neural Network [ $p=0.013$ ;  $p<0.05$ ]. A post-hoc analysis was then conducted, in which effect size was calculated to be 0.14. The classifications of effect sizes are traditionally small ( $d = 0.1$ ), medium ( $d = 0.5$ ), and large ( $d = 0.8$ ) (Sullivan, 2012). Under these guidelines, the effect size is small but not trivial.

Upon measuring the performance of the model through various mediums, it was ultimately determined that the Multi-Layer Perceptron was more effective for the problem at hand.

*Chi-Square Test:*

Tweets were separated into unigrams and bigrams, which were all stored into a vocabulary. A Chi-Square Test was completed on the tweets and their corresponding factors to determine stochastic variables, thus removing features that were irrelevant to classification.

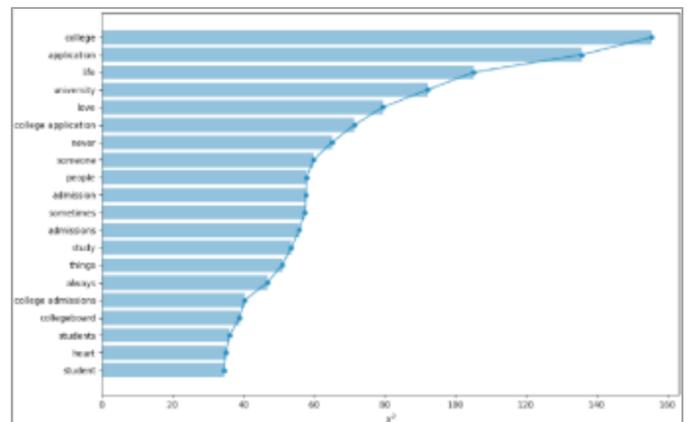
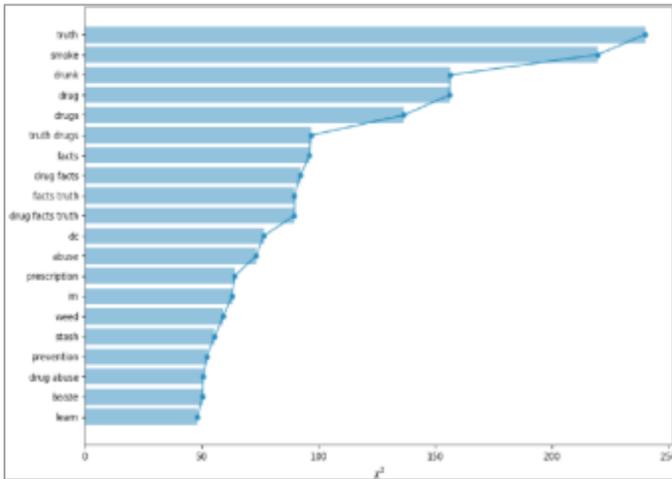


FIGURE 5: Academics

In the Figure 5, the most predictive word was “college.” The intercept chi-square value was

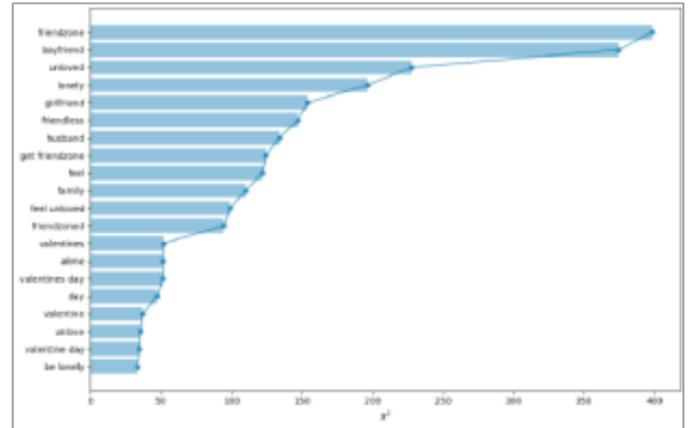


49.2. In Figure 6, the most predictive word was “truth.” The intercept chi-square value was 246.2. In Figure 7, the most predictive word was “body”, while the intercept chi-square value was 38.3. In the Figure 8, the most predictive word was “friendzone” with an intercept chi-square value of 27.3.

FIGURE 6: Drugs

FIGURE 7: Body Image/Appearance

FIGURE 8: Relationships



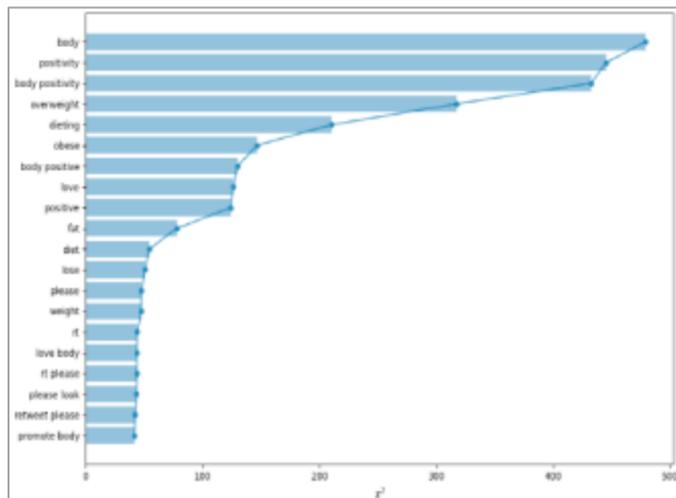
choice model that is aware of this bias and accounts for it by conforming to the independence of irrelevant views. The model was simulated through NLP techniques and assessed on participants for its influence on self-esteem.

A positive correlation was noted between the time exposed to the FreeFeed simulation and self-esteem scores. On the other hand, when users interacted with a model that mimicked recommendation systems, self-esteem scores decreased. After conducting statistical analysis, there was determined to be a significant statistical difference between the two simulations.

Conclusively, this work integrates elements from choice modelling, Bayesian inference, and self-esteem analysis to propose a novel idea that combats degenerate feedback loops in personalization systems.

**Discussion:**

In this paper, we researched degenerate preference systems, where users select options amongst a limited set of views. We propose a



**Conclusion:**

The FreeFeed model proved to have substantial benefit to user self-esteem, which indicates the potential for Bayesian choice models in the market. The harmful side-effects of self-reinforcing feedback loops necessitate the creation of models that investigate alternatives and learn to make the most optimal presentations. Our work can be further expanded to include a large sample size, further validating our findings and increasing the accuracy of our models. The model could also be assessed for its influence on

body image, suicide ideation, and depression. Nonetheless, our findings may lead to the development of more complex model architectures, as well as a deeper understanding of the influence that recommendation systems have on users.

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# From DIO2 Genotype to Personalized Medication

Jihong Jung

West Windsor-Plainsboro High School North, United States

jihongjung2004@gmail.com

## Abstract

Hypothyroidism is a syndrome in which the metabolic process of the entire body is degraded due to a lack of thyroid hormones. The single nucleotide polymorphism (SNP) information from the DIO2 gene found in the patient's genome is currently used in combination therapy: a treatment for hypothyroidism by providing patients with levothyroxine and liothyronine together. In patients with rs225014 (T→C) transition in DIO2, the conversion from prohormone thyroxine (T4) to bioactive thyroid hormone (T3) proceeds inefficiently even if the level of T4 is increased through Levothyroxine (LT4). However, there is a lack of information to explain how the SNP of DIO2 is linked with the effectiveness of the treatment, and some findings are incomplete and conflicting. In this study, we analyzed the cellular localization of the DIO2 gene, and investigated the tissue-specific gene expression of DIO2 in our body organs. We also conducted a gene network analysis of DIO2 to find the closely related genes to DIO2. Our result shows that the DIO2 gene is closely associated with eight proteins that function as Ubiquitin-dependent proteins. Thus, this study investigated for the first time that DIO2 functions as a homeostasis regulator for thyroid hormones and is closely involved in the proteolytic regulatory system by ubiquitin. The findings provide more information on DIO2 gene function, which can be applied to the development of personalized treatments for hypothyroidism, suggesting that the drugs can be prescribed more precisely and accurately.

*Keywords: Hypothyroidism, Personalized Medication, DIO2, Ubiquitination, Gene Network Analysis*

## Introduction

Hypothyroidism is a condition in which the thyroid gland cannot create enough thyroid hormone that humans need. This negatively affects general human metabolism such as gaining or losing weight, disrupting heart rate and body temperature, and weakening muscles. (1)

Out of thousands of medicines, the most frequently used medicine in the world is levothyroxine (LT4). (2) LT4 dosing normalizes T4, a hormone type of medicine that replaces mal-function hormones in the thyroid gland and helps our body remain at the thyroid hormone level. (3) T3, the metabolically active form, derives from extrathyroidal conversion of T4 by deiodinase 2 (D2) enzyme encoded by DIO2 gene. In thyroid-deficient patients, decreased levels of free T3 have been associated with the polymorphism rs225014 T/C in DIO2 (4)

There are two types of substitutions of nucleotide sequences of genes: mutation and single nucleotide polymorphism. Mutation occurs when there is an error during DNA replications which rarely occurs. It can affect the physical appearance of an organism. In contrast to that, single nucleotide polymorphism is more likely to occur in organisms and not all of them change the physical appearance of an organism. Still, it may

create unique characteristics of the organism. (5) Many scientists hypothesize that the unique characteristics created due to SNP would be why the patients with the rs225014 T/C on DIO2 suggested the combination therapy. (6)

Various SNPs exist in the DIO2 gene. However, one of the most significant SNP is rs225014. It is a type of SNP that occurs in DIO2, which encodes the (T) allele to the Thr (threonine) and (C) allele to the Ala (alanine). Encoding (T) allele to the Thr is more common than the (C) allele to Ala because more people tend to have (T) allele in their DIO2 sequences. It can cause various conditions such as osteoarthritis and psychological disorder. However, this SNP is significant to the study because it can cause thyroid hormone metabolism. The previous research indicated that hypothyroid patients who did not show much improvement using LT4 therapy tend to have lower brain thyroid levels which correlate to rs225014. (7) On the other hand, people with precedence of the rs225014 showed more improvement on the combination therapy. (8) In short, the presence of rs225014 seems to impact hyperthyroid patients' preference of the combination therapy.

The guidelines on T4 + T3 combination therapy were published in 2012. However, dissatisfaction with the outcome of T4 monotherapy remains high. The purpose of this research investigates the general information on DIO2 gene and protein networks. In addition, this study investigated that DIO2 functions as a homeostasis regulator for thyroid hormones and is closely involved in the proteolytic regulatory system by ubiquitin.

## Materials and Methods

### *DIO2 protein localization and tissue-specific expression*

The basic gene information was obtained from GeneCard. (9) The information on gene position, summary, protein information, and protein localization was provided. It provides a database

of human genes that provides concise genomic-related information with all known and predicted human genes. It also provides genomic, proteomic, transcriptomic, genetic, and functional information on all known and predicted human genes.

### *DIO2 functional protein association network analysis by STRING*

DIO2 functional protein association network was analyzed by STRING. (10) It is a database of known and predicted protein-protein interactions. The physical interactions and functional associations were analyzed from computational prediction. The interaction database was constructed based on the five main sources: genomic context prediction, high-throughput lab experiments, co-expression, automated text mining, previous knowledge in the database.

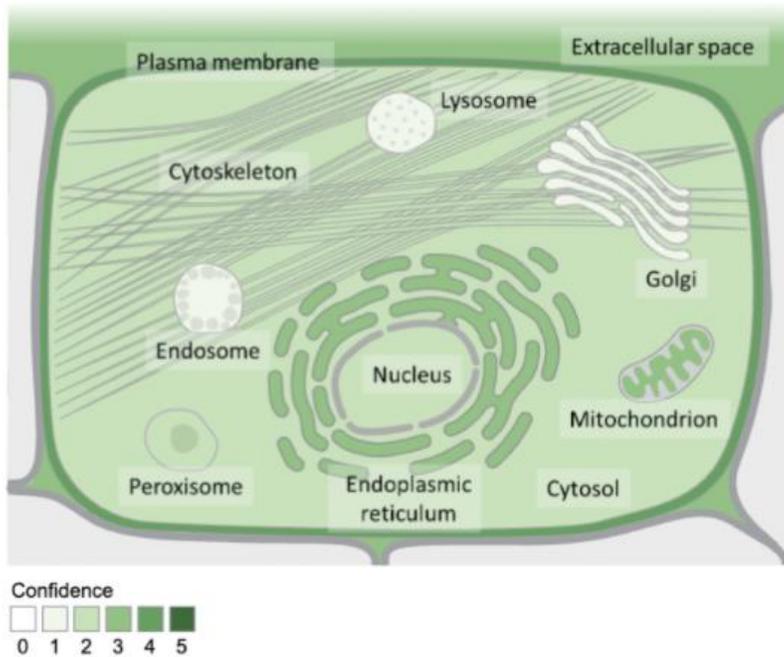
### *DIO2 associated proteins biological pathway analysis by GeneMANIA*

GeneMANIA predicts gene function by integrating multiple functional association networks. It predicts gene function from a single process-specific network using label propagation. It provides genome-wide predictions that achieve an accurate seed gene list without relying on a pre-specified association network. (11)

## Results and Discussions

Compartments program, a subcellular localization web database, was used to analyze the DIO2 protein subcellular localization. (12) This program predicts the protein subcellular localization based on the literature manual curation, microscopy-based screens, and predictions from primary sequence. The confidence scale ranges from one for low confidence to five for high confidence. DIO2 is predicted to be localized on the plasma membrane with a confidence level of four. It is also predicted to be localized on extracellular, mitochondria, and endoplasmic reticulum with a confidence level of three (Figure 1). Other places in a cell where DIO2 protein is being localized are

cytoskeleton, peroxisome, nucleus, cytosol, endosome, lysosome, and Golgi apparatus. This



Compartment	Confidence
plasma membrane	4
extracellular	3
mitochondrion	3
endoplasmic reticulum	3
cytoskeleton	2
peroxisome	2
nucleus	2
cytosol	2
endosome	1
lysosome	1
golgi apparatus	1

FIGURE 1. DIO2 protein subcellular localization analysis. DIO2 protein mainly localizes to the plasma membrane, extracellular, mitochondria, and endoplasmic reticulum.

shows how DIO2 protein is localized mostly everywhere in a cell, both inside and outside of it. However, the further cell experiment is needed to verify DIO2 subcellular localization in various types of human cells.

DIO2 tissue-specific mRNA expression was analyzed by RNA expression overview from the protein atlas database. It provides RNA-data from three different sources, respectively: Internally generated Human Protein Atlas (HPA) RNA-seq data, RNA-seq data from the Genotype-Tissue Expression (GTEx) project and CAGE data from FANTOM5 project, as well as the consensus dataset which is based on a combination of all three sources. (13) Color-coding is based on tissue groups, each consisting of tissues with

functional features in common. Figure 2 shows that DIO2 is mostly expressed in the thyroid gland and cervix uterine. The thyroid gland releases T4 thyroid hormones, which are necessary for our body cells to work properly. Since the main function of DIO2 is transitioning T4 to T3, high expression of DIO2 in thyroid gland may play an important role in producing T3 in human body. In the case of the cervix uterine, thyroid hormones are also necessary for its proper functioning. It regulates the metabolism and the development of ovarian, uterine, and placental tissues (14). As shown in both the thyroid gland and cervix, DIO2 is most likely to be expressed in organs that function within thyroid hormones.

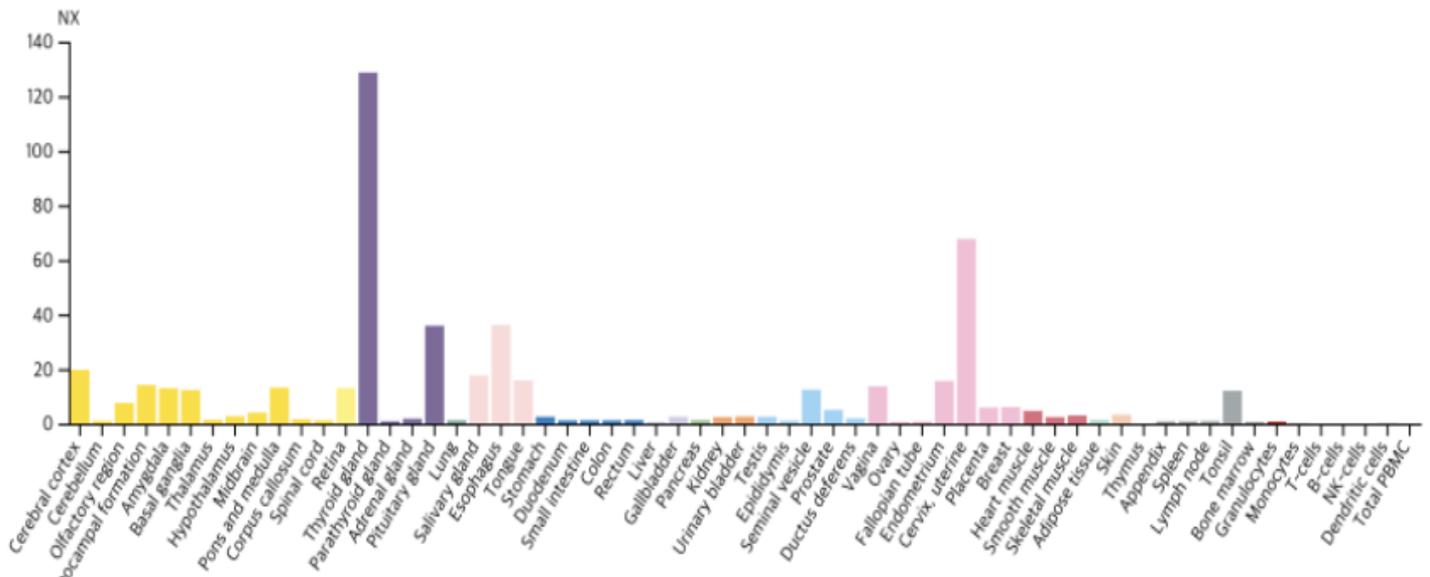
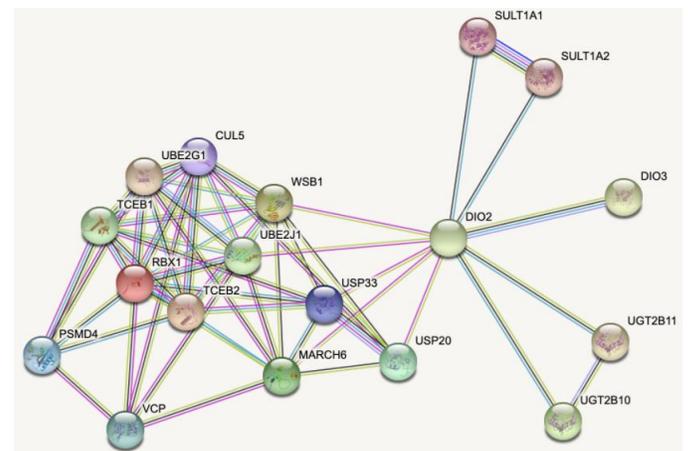


FIGURE 2. DIO2 gene is mainly expressed in the thyroid gland and cervix, uterine in human tissue. NX on the y-axis indicates the expression level.

To investigate the functional role of close relative genes of DIO2, we performed protein network analysis. Figure 3 shows 17 genes that are closely related to DIO2: CUL5, UBE2G1, TCEB1, RBX1, PSMD4, VCP, TCEB2, MARCH5, USP33, UBE2J1, WSB1, USP20, SULT1A1, SULT1A2, DIO3, UGT2B11, and UGT2B10. Identifying each one of their unique abilities and how it relates to DIO2 can bring new insights which can extend to existing studies. However, further analysis was required to find the novel relationship between DIO2 relative genes. To further investigate the biological pathway associated with these genes, 17 genes were used to analyze the protein physical interaction network and biological pathway in figure 4.

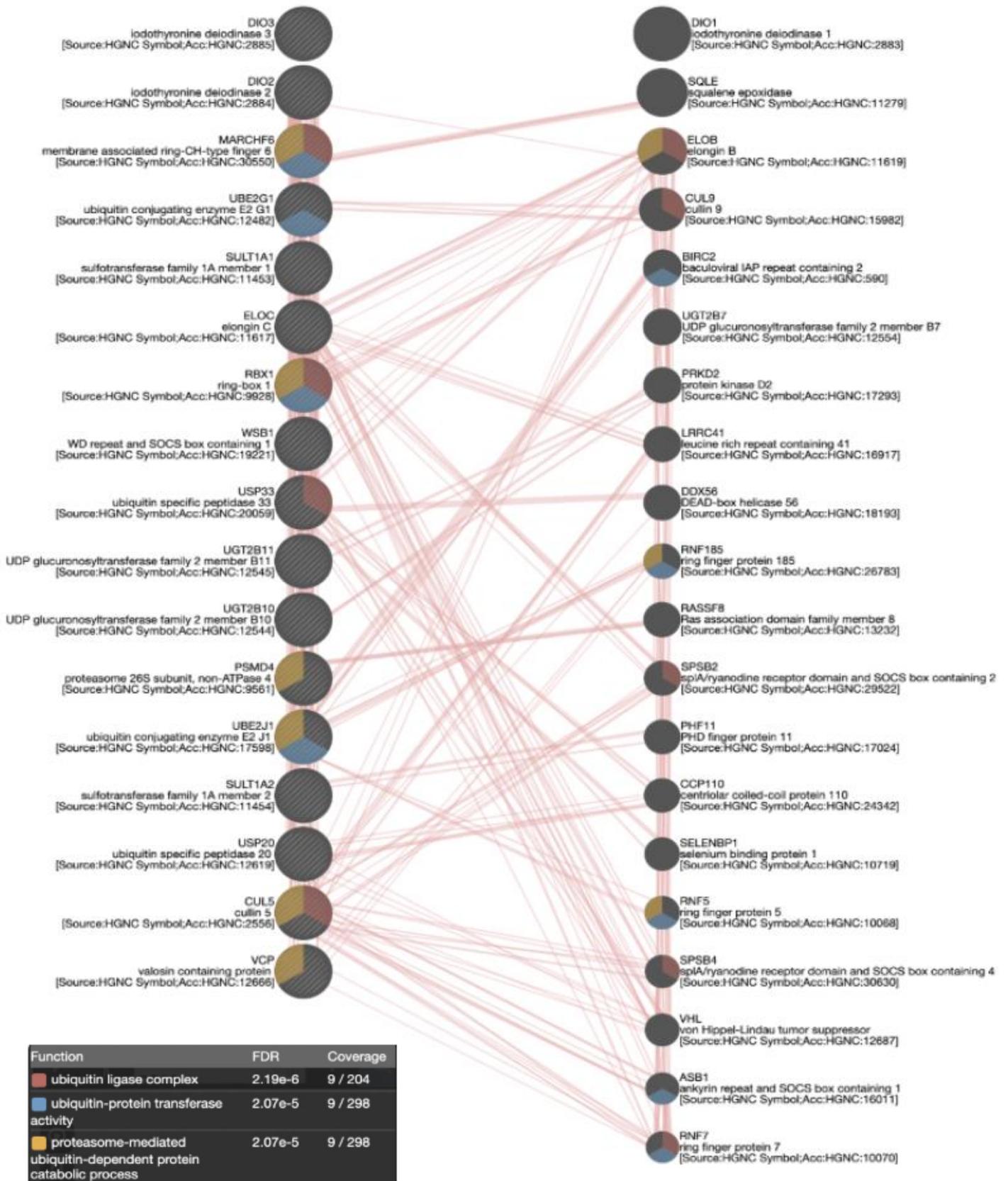
As shown in figure 3, more in-depth observation of those 17 genes is necessary. This figure provides closer observation on the relationship of those genes along with their protein. Figure 4 shows the graphical illustration of all 17 genes on the left column with the direct protein physical interaction and biological pathway. The red mark indicates the proteins associated with ubiquitin ligase complex pathways. The blue mark

indicates the proteins associated with the ubiquitin-protein transferase activity. The yellow mark indicates the proteins associated with proteasome-mediated ubiquitin-dependent protein catabolic processes. Interestingly, protein ubiquitin is involved in the relationships between those 17 genes. This is significant because it portrays a common protein that all those genes



contain, thus closely related.

FIGURE 3. Protein network analysis of DIO2 and associated network proteins.



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Figure 4. DIO2 protein physical interaction and biological pathway analysis. The red line shows the physical interaction of proteins within the selected proteins.

Ubiquitin plays a vital role in protein quality control and cellular regulation. Many proteins might be damaged by heat, oxidation, inherited mutation, heavy metals/metalloids, abnormal amino acids, or translation inhibition during and after protein synthesis. Ubiquitin helps these damaged proteins to be degraded through protein degradation, which is called protein quality control. Furthermore, ubiquitin can also degrade proteins that can impair cell cycle, transcription, DNA repair, stress responses, protein sorting, and apoptosis: this is called cellular regulation. By helping these proteins to go through protein degradation, ubiquitin is an essential factor in our body functions.

Next, the relationship between ubiquitin pathway and rs225014 polymorphism in DIO2 was investigated. The previous study indicated that D2, DIO2 encoded protein, is regulated to local thyroid hormone levels in the brain and other tissues. Therefore, increased activity of D2 is known to protect against hypothyroidism. This regulation is mostly brought about by substrate (T4)-induced ubiquitination (15). The DIO2 rs225014 polymorphism is positioned in exon 3 of the DIO2 gene resulting in a Thr92Ala amino acid substitution, which is closely linked to ubiquitination and a key determinant of turnover rate. (16) A recent report, which showed an association between CC genotype and osteoarthritis, showed that CC genotype decreased the activity of D2 in humans (17). Therefore, it is possible that Thr92Ala substitution may cause ubiquitination impairing that reduce the ability to maintain homeostasis of serum T3 level. In conclusion, these results are consistent with the previous findings that patients with CC genotype should be prescribed the T4+T3 combination therapy.

## CONCLUSION

This study prompts the new potential reasoning for why the presence of rs225014 in DIO2 in

patients affects the effectiveness of the combination therapy. Through the close investigations on DIO2, we were able to find how rs225014 in DIO2 might have affected the ubiquitination and lead to impair T3 hormones level. CC genotype in rs225014 may cause ubiquitination impairment of D2, which leads to reducing the ability to maintain homeostasis of T3. In conclusion, this study provides a novel protein interaction of DIO2, which may provide vital information for a more precise prescription for hypothyroidism patients.

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# How Cram Schools Perpetuate the Cycle of Poverty in South Korea

Haebin Jung

The American School in Japan, Japan  
22jungh@asij.ac.jp

## Abstract

The purpose of this research is to examine how cram schools perpetuate and exacerbate the cycle of poverty in South Korea. By examining a variety of data, including, but not limited to, college admissions statistics at the three most prestigious universities in South Korea (SKY), number and geographical distribution of cram schools, cram school prices, and housing prices, this paper identifies a connection between the market demand for cram schools among the top echelon households of South Korean society, and the admissions rates of their students to the most prestigious universities in the country. Cram schools, being an expensive commodity, lock many low-income students out of their services, consequently excluding them from the numerous benefits that come with a prestigious university education, including employment and the possibility of climbing the social ladder. These benefits are significant in South Korea, being a nation with a deeply ingrained prestige culture, which in the field of education, is demonstrated by means of heavy emphasis placed on the name value of one's alma mater.

*Keywords: Cram school, education, prestige, poverty, South Korea*

## Introduction

Looking down any street in Seoul, South Korea, one will find that there are cram schools everywhere. These cram schools, locally known as hakwon, offer various services, from academic tutoring to college admissions consulting, with the

intention to boost students' academic performances and move them a step closer to being admitted into a prestigious university. Cram schools are extremely high in demand, as Korean students compete for a limited number of spots at the nation's top-ranking universities. Admission primarily being based on performance on the College Scholastic Ability Test (CSAT), Korea's national college entrance examination, the competition is fierce: although approximately 500,000 students take the CSAT annually, only 3,000 acceptances are offered by Seoul National University, Korea's most prestigious university. A similar pattern can be observed with Yonsei University and Korea University, the second and third most prestigious universities in Korea, where half a million students compete for another mere 3,000 to 4,000 spots (Korea Institute for Curriculum and Evaluation, 2021). Abbreviated as SKY, these three universities are recognized in Korea for their name value and the unparalleled opportunities offered to their graduates. To receive admission, students must perform exceptionally well on the CSAT, which they attempt to achieve with the assistance of cram schools. Currently, in Korea, there are three primary forms of private tutoring. First, there is the classic hakwon, a for-profit learning institution. Students attend hakwons alongside attending formal schools. Hakwons are the most common and most demanded form of private tutoring, and naturally, heavily influence the education system in Korea. Other forms of private tutoring include individualized tutoring at a student's home, online courses, or self-study sheets that are delivered

and graded through mail (Kim & Lee, 2010). Cram schools are an expensive commodity, meaning many low-income families cannot afford them at all or can only afford those that are inexpensive and of lower quality, essentially locking low-income students out of the college admissions race simply due to their low socioeconomic status. This paper aims to explore how cram schools affect the Korean education system to exclude low-income students and perpetuate a cycle of poverty.

### **A Brief History of Education in Korea**

The Korean emphasis on test-taking stems back to Confucianism, a system of thought and behavior popularized in ancient China that spread its influence to adjacent Korea. Although the dominance of its ideologies has faded, many Confucian ideas and practices remain prevalent in Korean culture and daily life, especially in the field of education (Lee, 2006). In ancient China, candidates to serve in the state bureaucracy were selected based on their performance on civil service examinations, not on birth and status. Greater emphasis was placed on the ability to study and memorize, not on that to demonstrate creativity and critical thinking (Arbuckle & Talyor, 1995). This examination system spread its influence to neighboring countries, including Korea, where it continues to be an important aspect of Korean culture and daily life. Today, exams are extremely important for gaining admission to better-regarded schools and later, jobs; thus, a typical student's entire academic life is oriented towards preparing for necessary college entrance examinations (Lee, 2006).

The catalyst of the intense competition for admission into prestigious universities dates back to the 1950s, right after the end of the Korean War (1950-1953). President Lee Seung Man considered universal literacy and basic education to be vital in recovering from the Korean War. However, educational resources were scarce, and consequently, education was compulsory only up to the sixth grade. This changed when

General Park Chung Hee took over in 1961. Through strong government initiatives, Park led Korea to an unprecedented state of economic growth. The consequent increase in income along with the number of elementary school graduates led to an increase in demand for secondary education. Students desired to get into better-ranked middle and high schools, and as schools were allowed to select students through rigorous entrance examinations at the time, competition became fierce. To obtain an advantage in this competition, many students started turning to and relying on cram schools and other forms of private tutoring (Kim & Lee, 2010).

With the intention to fix this problem, the government launched the High School Equalization Policy (HSEP) in 1974. The HSEP eliminated entrance examinations and randomly assigned students to a high school nearby their residence. The HSEP was successful in eliminating competition among high schools, but failed to take into account that, regardless of their high school, students continued to want to enter more prestigious universities (Byun et al., 2012). Perhaps the government could foresee the devastating outcome that cram schools would bring upon not only the Korean education system, but the economy and society as well. In the 1980s, President Chun Doo Hwan outright banned all forms of private tutoring, reasoning that access to education should be more fair and affordable. However, the ban was lifted after just ten years, due to the exceeding number of individual tutors and cram schools that attempted to operate illegally (Choi & Choi, 2016).

Meanwhile, the government maintained a quota for the number of university admissions offers and mandated strict student selection procedures for all universities. All these government policies—HSEP, outright ban of private tutoring, and mandation of strict student selection procedures—although initially launched with the intention to reduce private tutoring, reversely ended up igniting mass “education fever” and increased private tutoring. University admissions

progressed to become extremely competitive, and the intensity of the competition has not ceased to this day (Kim & Lee, 2010).

Therefore, students and their families turn to exterior help to gain a competitive advantage in the admissions process. Currently, 69.2 percent of elementary school students, 66.7 percent of middle school students, and 60.7 percent of high school students participate in private tutoring (Statistics Korea, 2021).

A frequent criticism of the HSEP was that the policy prompted students' families to move to districts near traditional elite high schools, such as Gangnam and Seocho. These districts eventually established reputations for having high "education fever," and cram schools seeking opportunities to earn high profits started to move their locations to these districts. Families ambitious to get their children admitted into prestigious universities—which are most families in Korea—moved to these districts to better access cram schools and other educational opportunities. The demand to live in these districts soared; thus, house owners were incentivized to raise prices, as they recognized that prosperous families would be willing to pay extremely high costs to live in these districts to send their children to quality cram schools (Cho et al., 2020). Since then, house prices in Gangnam, one of the most affluent districts in Seoul at present, have continued to soar; the average housing cost in Gangnam is an exceedingly high \$1,671,585.35. As a means of comparison, the average housing cost in Seoul as a whole, is \$927,651.51 (Korea Real Estate Board, 2021).

Concurrently widening with the gap of housing costs is the gap of the number of cram schools in more and less affluent districts of Seoul. Now, Gangnam and Seocho are home to 2,455 cram schools, or 21.4 percent of all cram schools in Seoul. Accordingly, 5 out of 10 public high schools with the highest number of SKY matriculations are located in Gangnam and Seocho (Seoul Metropolitan Office of Education, 2021). The strong positive correlation between

the high number of cram schools and the high number of SKY matriculations shows the extreme concentration of prosperous families in Gangnam and Seocho—just two of 25 districts in Seoul—and the uneven socioeconomic and geographical distribution of admitted students (Seoul Solution, 2020).

### **Prestige Culture in Korea**

While the extreme number of students attending cram schools may seem absurd, families are willing to pay for the high costs of a cram school education, as the college one attends in Korea has a significant impact on their employment opportunities and socioeconomic status.

A major emphasis on prestige is put on students from an early age. Prestige is valued over skillset, and all students are ingrained with the idea that SKY universities are the three most prestigious universities in Korea and that graduating from one is essential in guaranteeing a stable future (Lee & Shouse, 2011).

SKY universities were the first universities to emerge after the creation of the modern higher education system in Korea. The roots of Yonsei University date all the way back to 1885, when the former institute of Severance Medical College and Hospital (part of Yonsei University) was established (Yonsei University, 2021). It was the first modern hospital and academic institution built in Korea. Ten years later, the former institute of Seoul National University College of Law was established, and another decade later, Bosung College (later renamed to Korea University) was established (Seoul National University, 2021; Korea University, 2021). SKY universities have produced countless notable alumni, from Ban Ki Moon, who served as the eighth Secretary-General of the United Nations, to Bong Joon Ho, an Academy Award-winning film director.

Due to their prolonged history and the notability of their alumni, SKY universities are considered to be extremely prestigious and a diploma from one is associated with significant benefits that essentially guarantee a path of success and

stability—better access to employment, and higher positions after employment. In fact, in 2016, 46.49 percent of high government officials and 50 percent of CEOs of major financial industries were graduates of SKY universities (Ha, 2016). The fact that graduates from three out of 203 universities in Korea are occupying nearly half of high-status positions in the two fields demonstrates the significant role the name value of one's alma mater plays in the workforce.

Furthermore, according to a survey distributed among SKY graduates by Incruit, a job recruitment website, 63.0 percent of respondents stated that it was easy to get employed due to their alma mater, and 36.5 percent of respondents stated that the reason why it was easy to get employed was due to networking and connections, as other SKY graduates were already employees in the company (Incruit, 2010). The fact that SKY's name value provides its graduates with better employment prospects, part of the reason being networking, serves as further validation that attending a SKY university truly has the potential to impact a person's life and, in some instances, help them climb the social ladder—if they can afford it.

### **Cram Schools and the Perpetuation of the Cycle of Poverty**

Although on average, households invest approximately \$300 in cram schools monthly, it is not uncommon to find households that invest a couple of thousand dollars in the service (Statistics Korea, 2021). The high costs of cram schools mean that only the higher echelons of Korean society are able to afford the service to its full extent, and get a head start in the college admissions race.

The CSAT, unlike many other standardized tests, heavily assesses a student's ability to memorize facts and figures, not on that to think analytically and critically. One cannot anticipate performing well on the CSAT solely through natural intelligence. The CSAT, an exam one must learn to take, exhibits a strong positive correlation

between the amount of time and money invested into preparation and performance on the exam (Kim & Lee, 2010).

Thus, students turn to cram schools to learn how to take the CSAT. Cram schools have access to confidential data about which passages and types of questions are likelier to appear on the exam, and instruct students on how to study for the exam most efficiently and what to focus on from the broad curriculum. Furthermore, the fast-paced and intense nature of instruction of cram schools allows students to get a head start on learning the content that is assessed on the CSAT, so that more time can be allocated to practicing and reviewing (Lee & Shouse, 2011).

Despite how essential cram schools are in preparing for the CSAT, in the end, cram schools are an expensive commodity, and many students cannot afford them or can only afford those of lower quality. As aforementioned, as those who perform well on the CSAT are those who invested the most time and money into preparing for the exam, low-income students who are unable to afford quality cram schools have practically no chance of performing well on the exam. Thus, as admission to SKY universities is primarily based on CSAT performance, by nature, the majority of admitted students are from high-income households. In fact, 80 percent of SKY universities students are from households with an annual income from the top 20 percent of Korean society, and do not apply for financial aid during their college years (Yi, 2017).

Even worse, as students continue to invest in exam preparation, the Korean Ministry of Education progressively increases the difficulty of the CSAT in order to be able to differentiate students based on their exam performance. If the CSAT was made easy, then more students would excel on the exam, and there would be more qualified students than there are spots available. Nevertheless, an increase in the difficulty of the CSAT means an increase in the reliance of students on cram schools to better prepare themselves for the exam (Moon, 2020). Cram

schools are heavily ingrained in Korean society as a place to depend on when preparing for practically any selective procedure.

The cram schools' proof as an influential mechanism on CSAT performance and the subsequent demand for cram schools incentivize cram schools to raise their prices. The demand for cram schools is close to inelastic, as families are willing to pay the necessary costs, however expensive that may be, to invest in a stable and successful future. In fact, cram school prices rose by 7.4 percent in the span of two years between 2015 and 2017 (Seoul Metropolitan Office of Education, 2021).

The heavy reliance on cram schools also means that students show low engagement at formal school, as they have already learned the content at cram school. And schools know this; formal schools expect most of their students to be attending cram schools, and do not cover a considerable portion of the curriculum. Alternatively, class time is dedicated to practicing and reviewing for the CSAT. Kim Suk Kyu, an uncommon Korean middle school student who does not attend cram schools, publicly spoke about how he was unable to answer questions on a school test as it was assessing content that had only been taught in cram schools (Kim, 2016). Evidently, cram schools are now the primary source of education. This leaves behind low-income students who cannot afford cram schools or can only afford those of lower quality, as they cannot prepare themselves for the CSAT solely based on formal school education. Not only does this plummet their chances of performing well enough on the CSAT to be admitted into a prestigious university, but they are also being deprived of their inalienable right to education. With cram schools dominating the education system, those who cannot afford the service to its full extent are unable to arrive at just the first step of advancing themselves up the social ladder, cram school, and are locked into a lower socioeconomic class before the race even begins. There is a rigid sequence of steps: employment

opportunities and a high socioeconomic status only come with a prestigious university degree, which only comes with an exceptional CSAT performance, which only comes with major investment in cram schools.

However, as desperate as they are to escape the cycle of poverty, low-income families spend up as much as 30 percent on their income on cram schools (Lee & Shouse, 2011). Note that the minimum wage in Korea is \$7.50, which amounts to an annual salary of \$18,815.45 (Minimum Wage Commission, 2021). To be willing to spend 30 percent of \$18,815.45 on cram schools for some, illustrates how a prestigious university degree is a primary way for one to raise their socioeconomic status in Korea. However, a survey by the Ministry of Education and the National Statistics Office showed that middle- and higher-income families spent five times more on cram school education than lower-income families (Kim & Lee, 2010). Even going as far as to spend 30 percent of their income is nowhere near what the rich are able to afford—quality cram schools with access to the best teachers from top universities and difficulty attained resources (Kim & Lee, 2010). An extensive economic and educational gap is prevalent, so prevalent to the extent where it is nearly impossible for a low-income student to even near a high socioeconomic status.

Perhaps if the CSAT assessed one's level of intelligence and ability to think analytically and critically, an economic and educational gap to such an extent would not have occurred, but instead, the CSAT being a test that assesses one's ability to simply memorize facts and figures, makes attending a cram school to prepare for the exam an undeniably major benefit.

For many families, the reality is that they cannot afford any supplemental schooling. Therefore, technical high schools in Korea tend to cater to low-income students, creating a widespread stigma that attending any type of technical high school is an indication that one is from a low-income household. Graduates from these

schools, unable to pay for cram schools, were never competitive applicants for SKY universities, and are often relegated to blue-collar jobs for life (Choi, 2021). Given the current structure of the education system, the social ladder is nearly impossible to climb.

## Conclusion

This paper has explored the connections between cram schools and poverty in Korean society. Different types of data ranging from college admissions statistics to survey results of SKY graduates regarding their employment prospects and the benefits of the name value of their alma mater were observed. This paper has also analyzed cram school-specific information, such as the concentration of expensive cram schools in affluent districts, as well as the alarming number of students enrolled in them. It is apparent from the data that the high demand of cram schools, resulting from ambition for prestigious tertiary education, causes students to rely on cram schools to gain an advantage in the college admissions process. As cram schools are extremely expensive, low-income students are largely unable to pay for the service and are locked out of a system that values a SKY education above all else. While this system is still heavily used in Korea, many students are noticing the injustices of this cram school culture, and are speaking up against it. In the college admissions process at large, there are plans to rely less on CSAT performance and more on extracurricular activities and involvement in the school community (Kong, 2018). These changes, if implemented, would be a step in the right direction; the admissions process, as it stands, is elitist. However, given Koreans' over-reliance on cram schools, it is possible that cram schools will evolve to cater towards extracurricular activities instead of exams. To create a more equitable higher education system, formal high schools should teach all students the entire curriculum, and college admissions should work towards being more holistic, taking into account a

students' socioeconomic status and the unique circumstances surrounding their application.

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# The Impact of Low Farming Yields in Sub-Saharan Africa on Maternal Mortality and Mortality of Children Under the Age of 5

Vinay Kalva

Skyline High School, United States of America  
workemail.vinay@gmail.com

## Abstract

Child and maternal mortality are major causes of morbidity and mortality in sub-Saharan Africa. Further, agriculture is a key part of the sub-Saharan African economy. However, the role of low farming yields in sub-Saharan African health outcomes has not been adequately considered, with only two studies having been conducted as of 2021. In this paper, the experimenter used publicly released data from UNICEF and the World Bank for all sub-Saharan African countries to determine the role that low farming yields had on maternal mortality and mortality of children under the age of 5 (MC5). The experimenter found a negative correlation between low farming yields and maternal mortality as well as low farming yields and MC5; however, the correlation was weak due to data heterogeneity. The two primary outliers, Mauritius and Cabo Verde, have high healthcare scores and high-quality health education respectively, which contributes to their low rates of maternal mortality and MC5. While this study did not find a positive conclusion, it adds to the literature by providing an opportunity for further research to explore the relationship between agriculture and health in sub-Saharan Africa, which has historically been understudied in the region and not studied previously on the scope of this paper.

Keywords: farming yields, child mortality, maternal mortality

## Introduction

Sub-Saharan Africa is among the world's poorest regions (Schoch & Lakner, 2020). While the region has improved its health, wealth, and agricultural statistics over the past two decades, agricultural changes have not been as large or impressive as predicted due to a lack of agricultural productivity (Jayne & Sanchez, 2021). Further, many have expressed concern that sub-Saharan Africa may not be able to produce enough food to meet the needs of the millions of people that reside in the region (van Ittersum et al., 2016). Adding to the region's challenges, the Lancet Commission on the Future of Health in Sub-Saharan Africa found that sub-Saharan African nations must implement major reforms by 2030 to improve health in the region (Agyepong et al., 2017). One important and effective approach to reducing disease burden has been information campaigns through commonly consumed media. Studies examining this approach (radio information campaigns) have found positive results for mortality of children under 5 (MC5) and maternal health behaviors in Burkina Faso (Murray et al., 2018; Sarrassat et al., 2018). However, the role of agricultural yields has not been adequately considered in preventing disease, with only two studies conducted on the relationship between low farming yields and MC5 and none conducted on the relationship between low farming yields and maternal mortality. Both MC5 studies were conducted in Burkina Faso,

with no studies examining populations outside of Burkina Faso (Belesova et al., 2017; Belesova et al., 2019). Agriculture is a key sector of sub-Saharan African economies that can be influenced (McCullough, 2017). Thus, the investigator set out to examine the impact of low farming yields on MC5 and maternal mortality in all sub-Saharan African countries generally to determine what role improving farming yields had on reducing MC5 and maternal mortality.

## Methods

### *Dataset & Sample Size*

In this paper, the experimenter used existing maternal mortality and MC5 data in individual sub-Saharan African countries. All countries in sub-Saharan Africa (n=48) were examined in both maternal mortality and MC5 analyses.

### *Data Sources*

**MC5 and Maternal Mortality Data:** MC5 and maternal mortality data was obtained from two custom data warehouse spreadsheets produced by UNICEF. (UNICEF, n.d.-a; UNICEF, n.d.-b) This dataset consists of data collected by the World Health Organization, UNICEF, the UN Population Fund, the World Bank, and UN Population Database and brought together by UNICEF. The maternal mortality data was available from 2016, 2017, 2018, and 2019. (UNICEF, n.d.-a) The MC5 datasheet contained data for the years 2016 and 2017. (UNICEF, n.d.-b) All data was used under a CC-BY 3.0 license.

**Crop Yield Data:** Crop yield information was obtained from a World Bank dataset. (World Bank, n.d.) Crop yield data was provided from 1990 to 2018, in the years 1990, 2000, 2011, 2012, 2013, 2014, 2015, 2016, 2017, and 2018. All data was used under a CC-BY license.

### Definitions

*Maternal* mortality refers to deaths of females during pregnancy, childbirth, or post-natal for every 100,000 births. MC5 refers to deaths of children under the age of 5 per 100,000. Farming

yields refer to, in this paper, cereal crop yields in sub-Saharan Africa as defined by the World Bank (kilograms per hectare). Sub-Saharan Africa is a region containing the countries of Angola, Benin, Botswana, Burkina Faso, Burundi, Cabo Verde, Cameroon, the Central African Republic, Chad, Comoros, the Democratic Republic of the Congo, the Republic of the Congo, Côte d'Ivoire, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, São Tomé and Príncipe, Senegal, the Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Sudan, Tanzania, Togo, Uganda, Zambia, and Zimbabwe. (World Bank, n.d.)

### *Data Analysis*

Data analysis was conducted in Microsoft Excel. Raw data from UNICEF and the World Bank was sorted into several spreadsheets in Microsoft Excel. A grand total of 8 different spreadsheets were used: 3 spreadsheets stored raw maternal and child mortality data, while the remaining 5 spreadsheets were used to sort and examine the data. Of these 5 spreadsheets, 3 contained data for farming yields, MC5, and maternal mortality individually; the remaining 2 contained farming yield and maternal mortality data as well as farming yield and MC5 data. Trendlines and their respective equations in Figures 2A-2C were created using Microsoft Excel's scatterplot features (data was added to the respective area, and x- and y-axes were created such that the x-axis signified crop yields [see Definitions] and the y-axis signified the health indicator [MC5 or maternal mortality]).

## Results

Farming yield data was found for all sub-Saharan African countries except Equatorial Guinea and the Seychelles. Under-five and maternal mortality data was found for all sub-Saharan African countries. Data for all sub-Saharan African

countries and a comparison with the sub-Saharan African average are shown in Figures 1A-1C. All original data is found in Table 1. These data were derived from the World Bank and UNICEF as mentioned in the Methods section of this paper.

Country	Farming Yield Data	MC5 Data	MM Data
Angola	754.7	80.62230214	241
Benin	1405.4	95.13307868	397
Botswana	320.7	43.78164158	144
Burkina Faso	1009	93.86290945	320
Burundi	1048	61.34873273	548
Cabo Verde	157	16.83571002	58
Cameroon	1682.8	80.81870055	529
Central African Republic	907	117.4709876	829
Chad	825.2	121.50835	1140
Comoros	1364.9	67.32861972	273
Congo, Dem. Rep.	769.4	90.76392438	473
Congo, Rep.	826.2	50.90423184	378
Côte d'Ivoire	2254.7	85.2824024	617
Equatorial Guinea	N/A	87.67384977	301
Eritrea	644.5	43.28047615	480
Eswatini	1163.1	62.32347248	437
Ethiopia	2512.6	55.83953932	401
Gabon	1599.1	45.10712286	252
Gambia	847.6	55.71169433	597
Ghana	1907	50.02845666	308
Guinea	1158.7	103.2265284	576
Guinea-Bissau	1254.7	84.2230564	667
Kenya	1632.9	46.42323611	342
Lesotho	987.2	88.70980547	544
Liberia	1059.5	87.91427497	661
Madagascar	4302.1	54.12789836	335
Malawi	1903.1	46.86405848	349
Mali	1530	101.0624223	562
Mauritania	1361.2	77.79046189	766
Mauritius	5234.8	14.85838858	61
Mozambique	817.1	79.3896324	289

Namibia	426.3	44.52817149	195
Niger	541.9	86.64145094	509
Nigeria	1408.8	122.798947	917
Rwanda	1283.5	37.47282704	248
Sao Tome and Principe	2042.1	32.02913991	130
Senegal	1275	48.78242725	315
Seychelles	N/A	14.71213713	53
Sierra Leone	1143	118.2221809	1120
Somalia	551.9	124.3934416	829
South Africa	5644	35.59544333	119
South Sudan	734.5	96.22929869	1150
Sudan	584	62.16602409	295
Tanzania	1547.9	71.31723539	524
Togo	1139.2	50.24859619	396
Uganda	2047.2	53.75319205	375
Zambia	2479.4	64.33790066	213
Zimbabwe	622	58.23492444	458

TABLE 1: Original Data for Farming Yields, MC5, and Maternal Mortality.

Sub-Saharan African averages are mentioned in the Results text. Abbreviations and non-Anglicised names: MM = maternal mortality; Congo, Dem. Rep. = Democratic Republic of the Congo; Congo, Rep. = Republic of the Congo; Côte d'Ivoire = Ivory Coast

#### *Farming Yield Data Comparisons*

Of the countries in sub-Saharan Africa with farming yield data (n=46), 15 countries had higher farming yields, measured in kilograms per hectare, than the sub-Saharan African overall crop yield of 1457.6 kg/hectare in 2017. (Figure 1A) South Africa, Mauritius, and Madagascar had the 3 highest farming yields in the region. The 3 countries with the lowest farming yields (excluding the Seychelles and Equatorial Guinea, which did not have farming yield data) were Namibia, Botswana, and Cabo Verde. (Figure 1A)

#### *MC5 Data Comparisons*

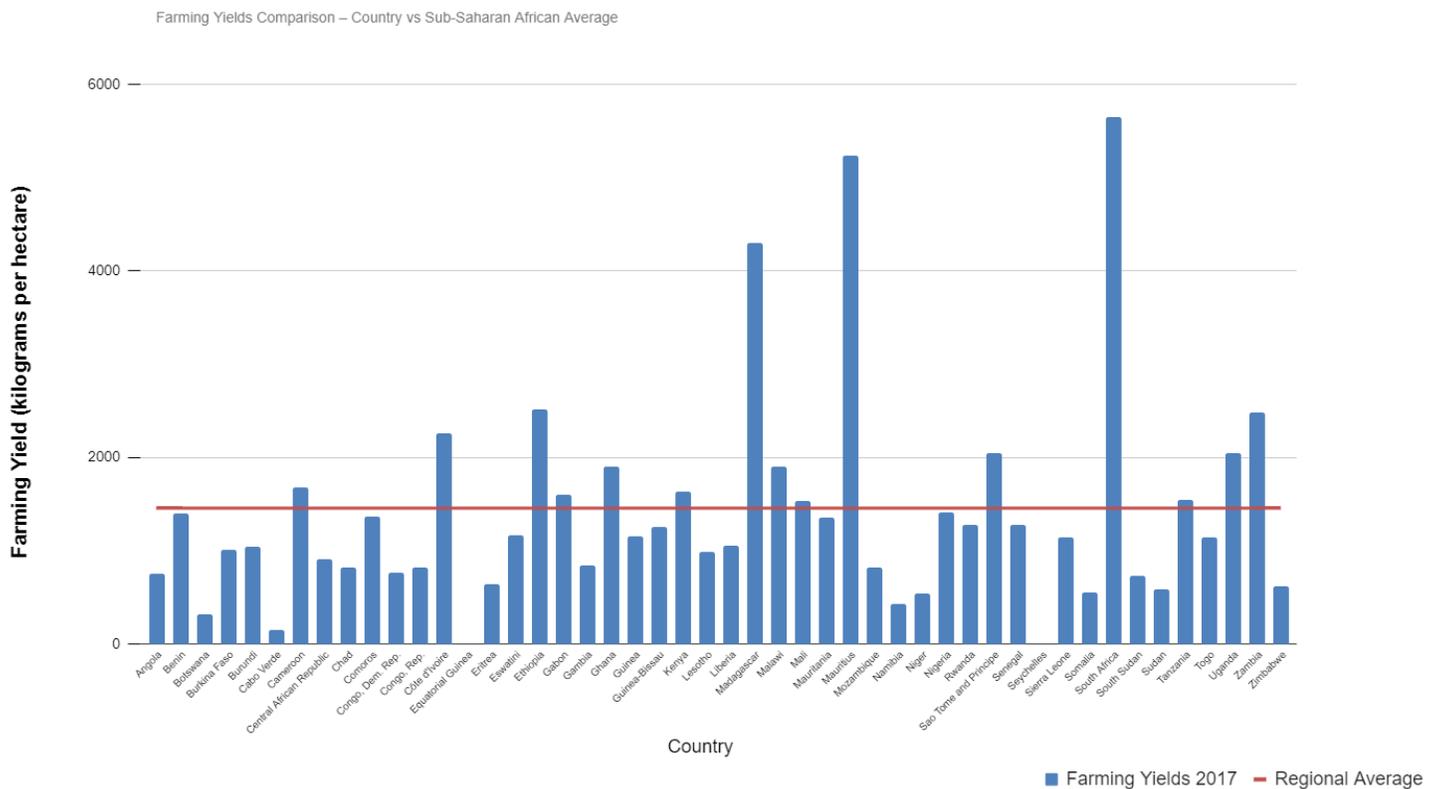
All countries in sub-Saharan Africa were included in this comparison (n=48). The 3 countries with the lowest MC5 were the Seychelles, Mauritius, and Cabo Verde; the 3 countries with the highest 100,000, with roughly 80.7 MC5 per 100,000. (Figure 1B)

MC5 were Somalia, Nigeria, and Chad. (Figure 1B) Angola had the MC5 closest to the sub-Saharan African average of roughly 80.6 MC5 per

*Maternal Mortality Data Comparisons*

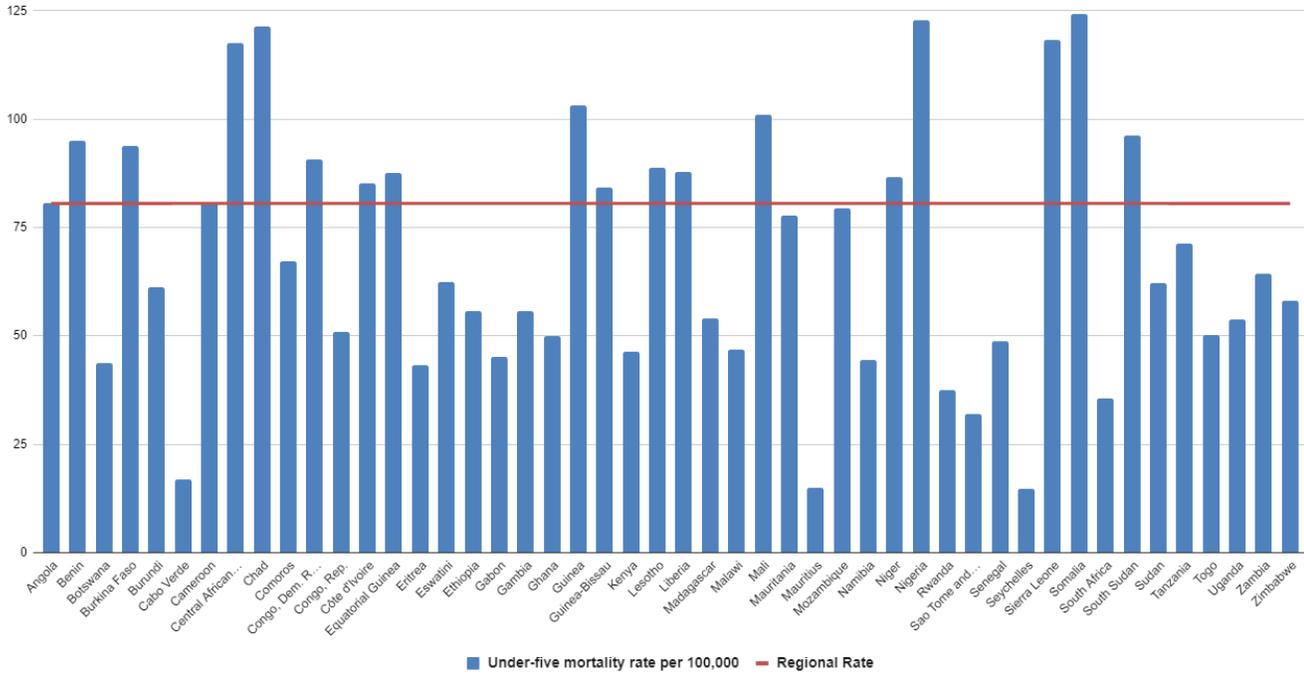
All countries in sub-Saharan Africa were included in this comparison (n=48). The 3 countries with the lowest maternal mortality were Mauritius, Cabo Verde, and the Seychelles. (Figure 1C) The 3 countries with the highest maternal mortality were Sierra Leone, Chad, and South Sudan. (Figure 1C) The sub-Saharan African overall maternal mortality rate is 533 per 100,000, and 15 countries had higher maternal mortality rates than sub-Saharan Africa as a whole.

FIGURE 1: Country comparison with regional data



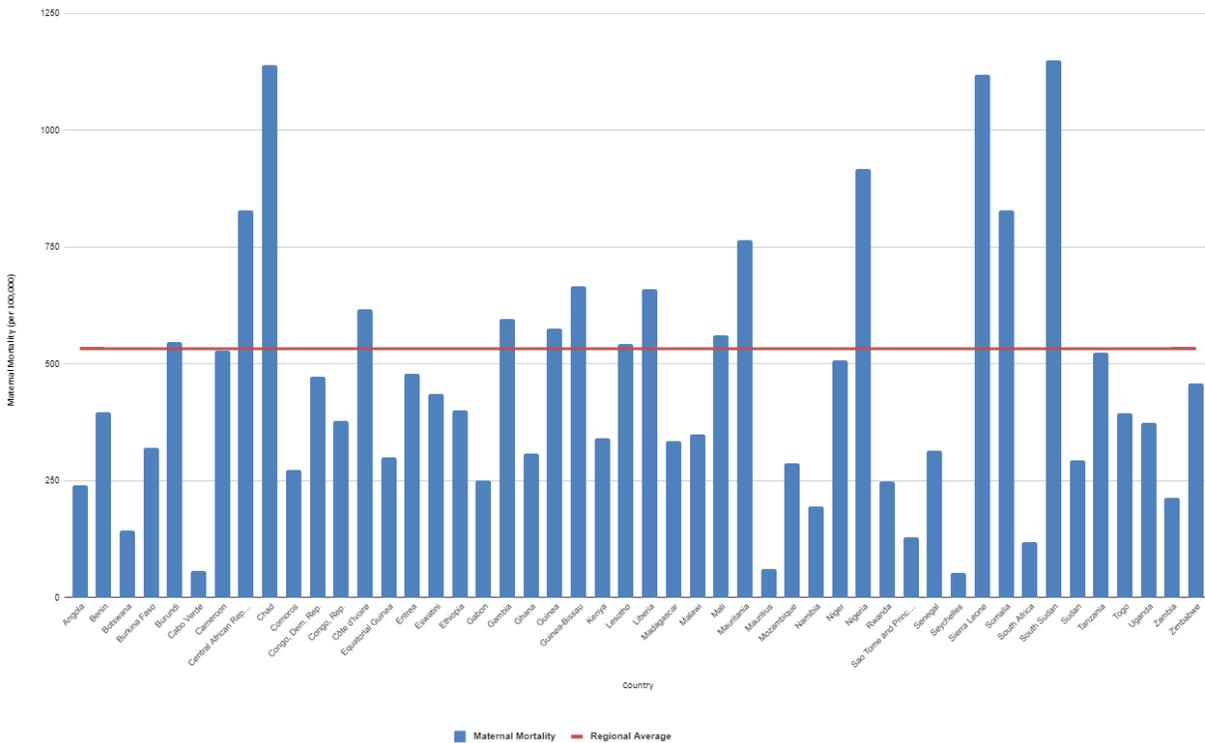
(A) Farming yields (cereal yields in kg/hectare)

Under-five Mortality Rate per 100,000 – Country-Regional Comparison



(B) MC5 per 100,000

Maternal Mortality Comparisons – Sub-Saharan Africa vs Individual Countries



(C) Maternal mortality per 100,000 births

### Low Farming Yields and Maternal Mortality

In order to examine the existence of an association between low farming yields and maternal mortality, I used Microsoft Excel™ to create a scatter plot with all data from countries with farming yield and maternal mortality data (n=46). I found a negative correlation between an increase in farming yields and a decrease in maternal mortality. (Figure 2) However, the statistical coefficient of determination is 0.095169864, indicating that this correlation is a weak fit.

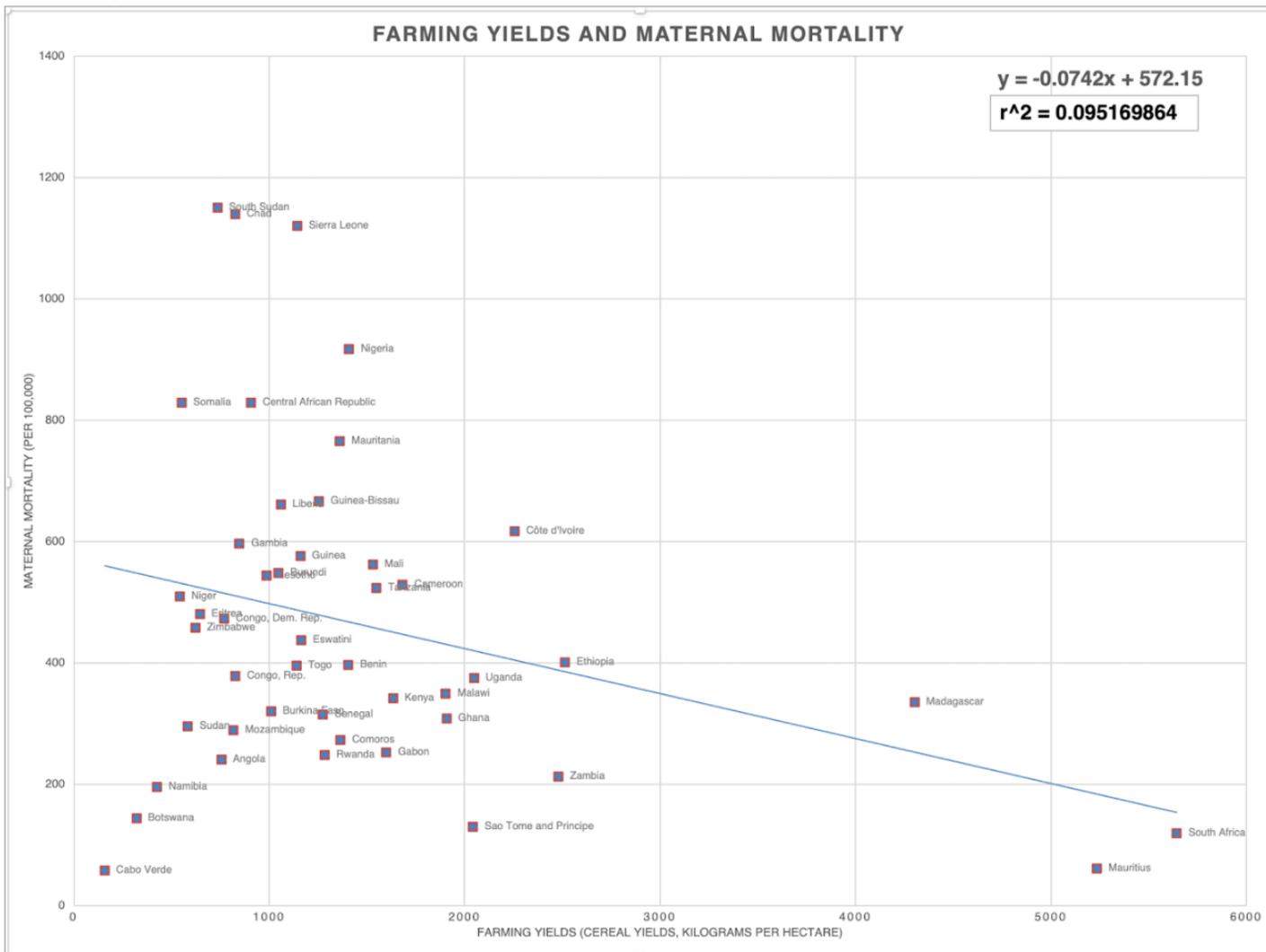


FIGURE 2: Scatterplot of Farming Yields and Maternal Mortality excludes sub-Saharan Africa average, Equatorial Guinea, and the Seychelles

*Low Farming Yields and MC5*

In order to examine the existence of an association between low farming yields and MC5, I used Microsoft Excel™ to create a scatter plot with all data from countries with farming yield and MC5 data (n=46). I found a negative correlation between an increase in farming yields and a decrease in MC5. (Figure 3) However, the statistical coefficient of determination is 0.117151635, indicating that the correlation is a weak fit.

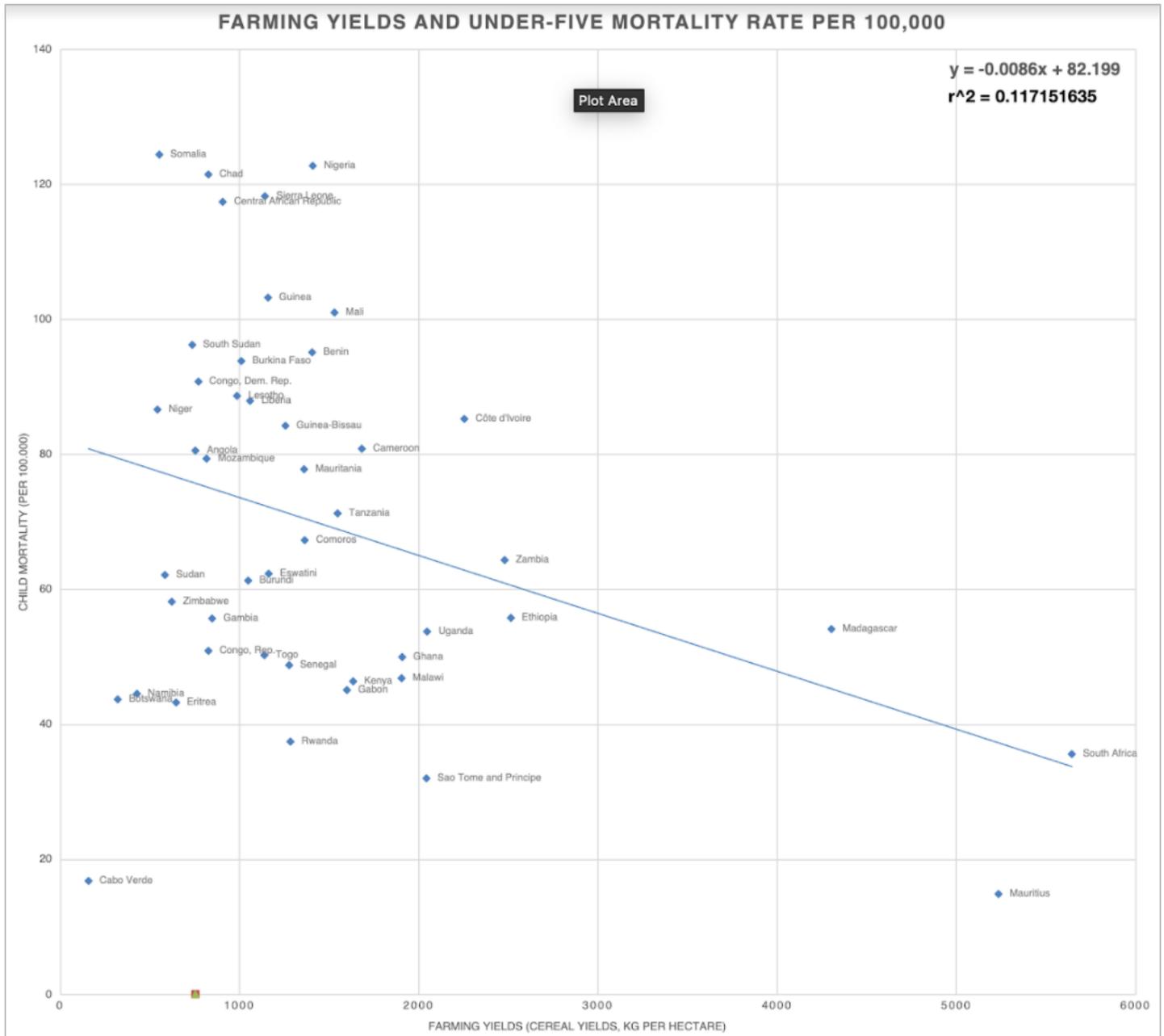


FIGURE 3: Scatterplot of Farming Yields and MC5 excludes sub-Saharan Africa average, Equatorial Guinea, and the Seychelles

## Discussions

In this paper, I examined data from UNICEF and the World Bank to determine the relationship between low farming yields and maternal and MC5. I found negative but weak correlations, indicating that low farming yields, across sub-Saharan Africa, do not affect MC5 and maternal mortality much. However, as with many analyses with large sample sizes (n=48), there were several outliers. Notably, Cabo Verde has low farming yields (157 kg/hectare) as well as low maternal and MC5. In cross-country comparisons, Cabo Verde was among the three nations with the lowest maternal and MC5. Mauritius fits a correlation between high farming yields and low maternal and MC5, with among the highest farming yields and among the lowest maternal and MC5. This suggests that Mauritius and Cabo Verde have completely different results than other sub-Saharan African nations due to other factors. Measures that Result in Lower Maternal and MC5 In 2015, Bauserman et al. examined individuals in the Global Network for Women's and Children's Health Research Maternal and Neonatal Health Registry, obtaining data for more than 270,000 pregnancies and 400 deaths across 6 different countries in South America, Africa, and Asia (Bauserman et al., 2015). Bauserman et al. found that hemorrhage and hypertensive disorders in pregnant females, which are treatable and manageable, should be managed to save lives. Further, Fenta and Fenta used regression modelling to determine the role of preventive measures for the prevention of general child mortality. Fenta and Fenta found that education, contraceptive use, higher age of mother at time of birth, birth at a public or private institution, and living in an urban area reduced the risk of MC5. This means that healthcare access can play a role in reducing both maternal and MC5 (Fenta & Fenta, 2020). Mauritius, one of the key outliers, has a high-quality healthcare system, suggesting that healthcare access and quality are causal factors.

### *Healthcare as a Causal Factor*

This is more likely in functioning healthcare systems with capacity and functionality. The 2021 World Health Statistics, published by the World Health Organization, show that Mauritius has had above-average healthcare functionality from 2015 to 2020, and ranks as the best in functionality and second-best in coverage in the WHO African Region (World Health Organization, 2021). This is corroborated by Mauritius having a Healthcare Access and Quality Index score of 69 in an analysis by the Global Burden of Disease 2016 Healthcare Access and Quality Collaborators (Fullman et al., 2018). Thus, it is plausible that Mauritius has low rates of maternal and MC5 due to a high quality of healthcare. However, this cannot be applied broadly. The opposite is true for Cabo Verde, which has a healthcare score of 55, lower than Mauritius. Thus, Cabo Verde is another outlier, similar to Mauritius, except in a different manner, as the country also ranked highly in MC5 and maternal mortality rankings (among the lowest maternal and MC5 in sub-Saharan Africa).

### *Education as a Causal Factor*

While Cabo Verde still lacks in its healthcare infrastructure, as is evident by its healthcare score, WHO Africa reports that the country has made significant improvements in health, increasing life expectancy especially (WHO Regional Office for Africa). Further, while Cabo Verde lacks hospitals, the country has a high literacy rate, which has eased the burden of spreading health-related information and has contributed to better results for Cabo Verde (WHO Regional Office for Africa). Thus, the low rates of maternal and MC5 can plausibly be attributed to high literacy and education rates as well as a relatively high degree of healthcare quality in the country. However, due to a low score on the HAQ Index, healthcare is not the primary causal factor; rather, education is.

### *Strengths and Limitations*

The strengths of this study are the large sample size and scope as well as its novelty. This study contributes to the field by providing a detailed analysis of a correlation between farming yields and maternal mortality and farming yields and MC5. As a result, it represents an area that can be further examined to draft policies that can better reduce the burden of maternal mortality and MC5.

Nevertheless, this study has its limitations. For example, no data was available for the Seychelles and Equatorial Guinea. This prevented a thorough analysis for all sub-Saharan African countries, as both were excluded to test the hypothesis most accurately. Second, the data did not account for underreporting, which is a significant issue in sub-Saharan Africa in particular. Third, the farming yield and MC5 data were available until 2019, but the maternal mortality data were only available until 2017. For consistency reasons, the experimenter chose to use 2017 data. However, this limited the applicability of the data to 2021 due to no fault of the experimenter.

## Conclusion

In conclusion, the experimenter found a negative correlation between low farming yields and MC5 and maternal mortality in sub-Saharan Africa. However, both correlations were too weak to produce any meaningful result across the region of sub-Saharan Africa. Nevertheless, this study provides a novel result for further research to examine individual countries in more detail and with more accurate statistical approaches. Further, this study provides an opportunity for future research to explore the relationship between low farming yields and health outcomes in sub-Saharan Africa, as well as the relationship between causes of low farming yields and health outcomes in sub-Saharan Africa.

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# In Silico Analysis of an Epitope-Based Bladder Cancer Vaccine

Sungjoon Kang

Korea International School, South Korea

sungjooneng@gmail.com

## Abstract

Bladder cancer is a malignancy that arises from the tissues of the urinary bladder and is one of the most prevalent cancers worldwide for which there is no cure. Previous investigations have determined that amyloid-beta precursor protein (APP) is overexpressed in bladder cancer and has a significant role in its malignancy. In an effort to speed up cancer vaccine development and offer a probable immunotherapy option, we decided to work on the in silico development of a vaccine that targets APP and thus bladder cancer. The secondary structure of APP was analyzed, and immunogenic B cell and T cell epitopes were predicted. These epitopes were further evaluated for MHC 1 and 2 binding, allergenicity, and toxicity. The C-ImmSim server was used in two different immune response simulations to target the complete APP protein and each predicted epitope. Our results demonstrate that APP is a good candidate target protein that, if administered along with an adjuvant, can elicit a strong immune response against bladder cancer.

*Keywords: In silico, bladder, cancer, vaccine*

## Introduction

### *Cancer*

Bladder cancer is a malignancy that arises from the urinary bladder tissues and is one of the most prevalent cancers worldwide (Chen et.al., 2017). According to Bray et.al. (2018), there were 549,393 new cases reported in 2018, and about 12,000 men and 4,700 women died from the

disease. The main types of bladder cancer are: 1) urothelial carcinoma and 2) squamous cell carcinoma. Urothelial carcinoma occurs in the urothelial cells that line the inside of the bladder, while squamous cell carcinoma commonly occurs in the lateral wall and trigone. The trigone is a triangular area formed by three openings in the floor of the urinary bladder located within the fundus (Jones, 2020).

There are 5 main stages in bladder cancer that range from stage 0 to stage 4. In Stage 0, abnormal cells are localized within the inter-tissue lining of the bladder. Stage 1 is characterized by the spread of the malignant cells into the inner lining of the bladder. Stage 2 involves the metastasis into the muscular layer of the bladder (Kaseb, 2021). In stage 3, the neoplasm has usually invaded the adipose tissue that surrounds the bladder, reproductive organs, and/or pelvic lymph nodes. Stage 4 is characterized by the metastasis to distant tissues or organs by way of the lymph nodes surrounding the common iliac arteries (Kaseb, 2021).

### *Treatment*

Currently, bladder cancer is treated using one of three traditional methods: surgery, radiation therapy, and/or chemotherapy (DeGeorge et.al., 2017). The most common types of surgery are transurethral resection and radical cystectomy. Transurethral resection is where a cystoscope is inserted through the urethra and into the bladder to remove any tumors. Radical cystectomy is

surgery to remove the bladder. For men, the prostate and seminal vesicles are also removed along with the bladder, while in women, the uterus, ovaries, and part of the vagina is often removed along with the bladder (DeGeorge et.al., 2017). Radiation therapy utilizes high doses of radiation to destroy or shrink cancer cells; however, this process is also detrimental to normal cells in treatment. Chemotherapy uses powerful chemicals to kill hyper proliferating cells by damaging the cell's control center that helps it divide, therefore interrupting the chemical processes involved in cell division, but it also has deleterious effects on normal cells (DeGeorge et.al., 2017).

*Protein*

Amyloid-beta precursor protein (APP) is a 120 kDa polypeptide whose current speculated function within the bladder is to bind to other proteins on the surface of cells and aid in cell-to-cell adhesion. This protein is highly conserved among mammals, as seen in this phylogeny tree where four species were chosen, and it was determined that the squirrel monkey had the closest similarity to humans (Figure 1). Below is a structural analysis of APP that shows its strands, helices, and coils (Figure 2). According to the Entrez database, APP is expressed within a wide range of tissues, but has a high expression rate in the human brain (Figure 3).

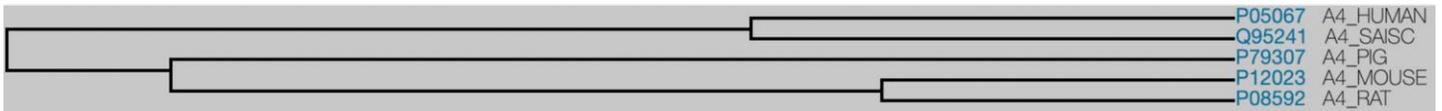


FIGURE 1: Phylogeny tree of Amyloid-beta precursor protein. The phylogeny tree showed the squirrel monkey to be the closest to humans followed by the pig, mouse, and rat.

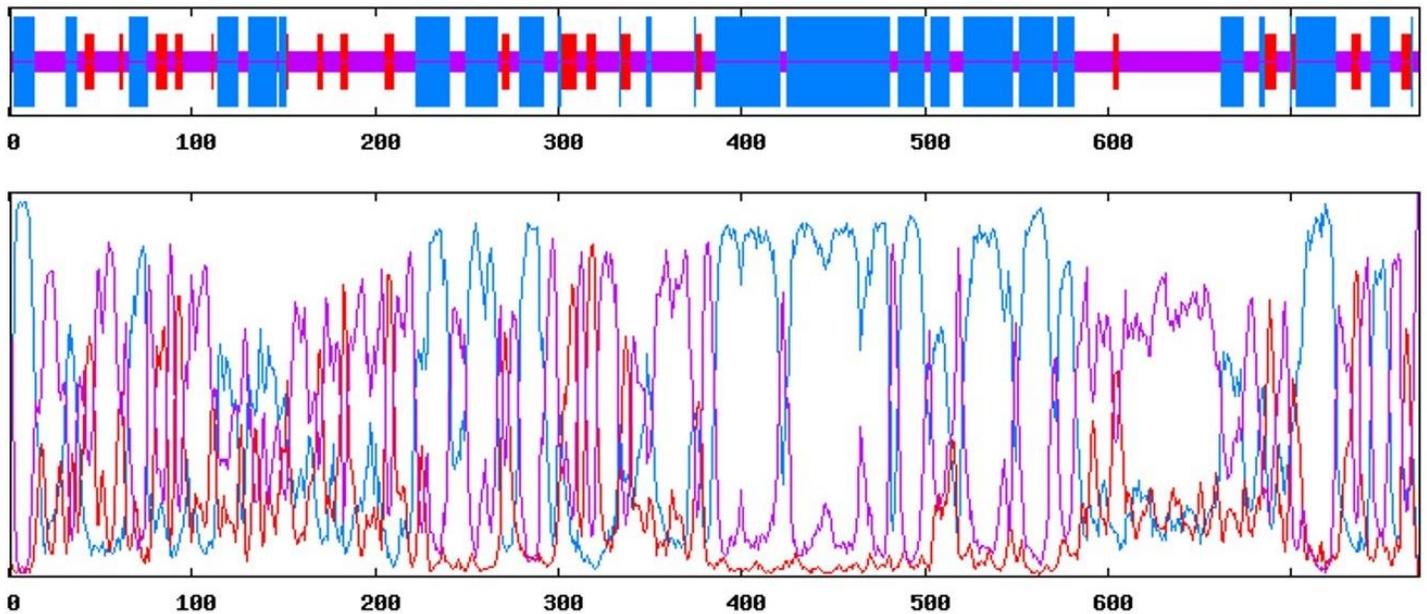


FIGURE 2: APP structure analysis. The secondary structure of the APP protein was analyzed using the Prabi server. The red are extended strands; blue are alpha helix configurations; and purple are random coils.

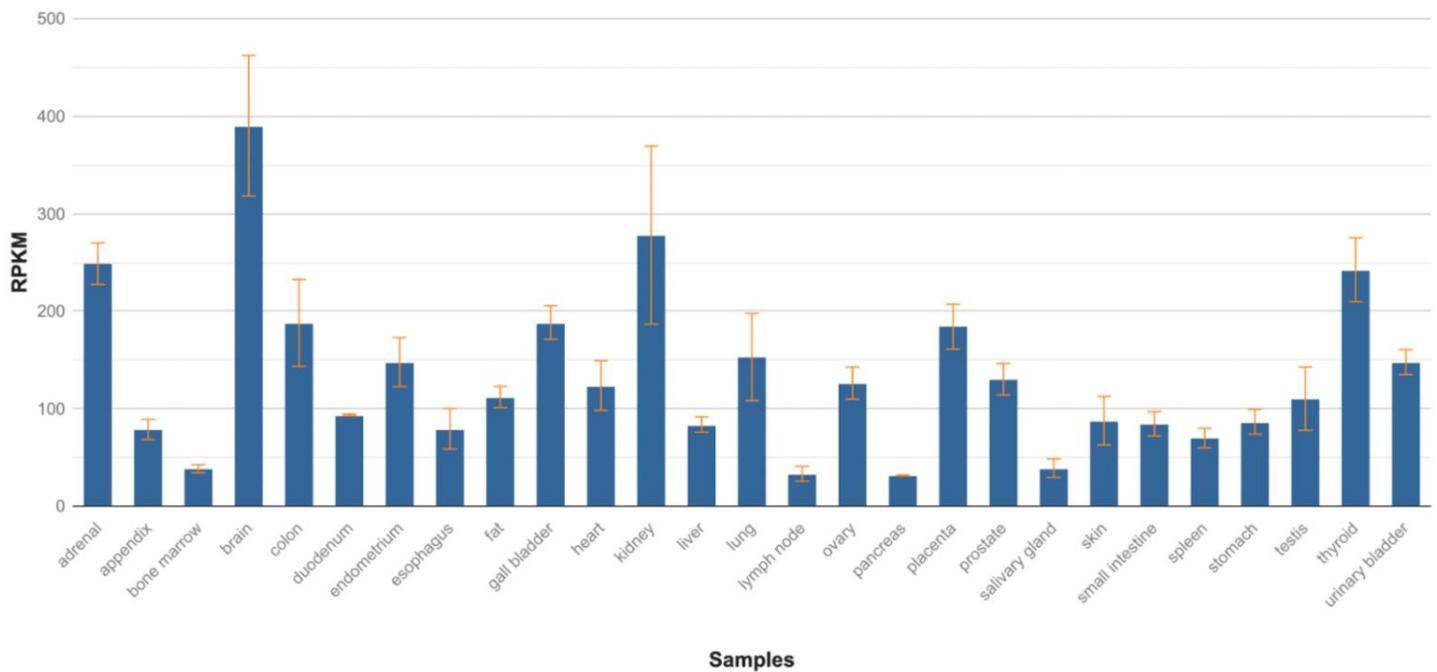


FIGURE 3: APP expression levels in the human body. Graph showing the varying APP expression levels in different tissues (NCBI, Entrez).

### *In Silico*

In silico methods allow for the computational development of new vaccines that may ultimately save on time and money. For example, in the recent COVID-19 pandemic, to quickly create a vaccine to target a novel virus, an in silico approach for its development was employed by numerous pharmaceutical companies. In silico trials helped predict therapeutic failures while minimizing undesired effects and these tactics allowed the COVID-19 vaccines to become the fastest vaccines ever developed (Russo et.al., 2020). These methods can also be employed in the development of a vaccine against bladder cancer.

### *Vaccine*

Previous studies have determined that immunization against a tumor-specific protein can elicit a targeted autoimmune attack that may provide protection and therapy against tumors (Tuohy et.al., 2016). Other investigations have determined that APP is overexpressed in bladder cancer and has a significant role in its malignancy

(Zhang et.al., 2018). To speed up vaccine development and offer an immunotherapy option, we decided to work on the development of a vaccine that targets APP and thus bladder cancer. This vaccine might help strengthen the body's natural oncologic defenses against the cancer and it could also be administered as adjuvant therapy in conjunction with or after standard surgical and chemotherapeutic approaches.

### **Methods**

#### *Protein Sequence*

Once a target protein was identified through an initial search, NCBI's Entrez database was accessed to obtain APP's accession number (NP\_000475.1), FASTA sequence (Figure 7), and locus (21q21.3). The given APP transcripts were obtained along with the positions using NCBI's Spleign (Table 1). The 3D structure of APP was generated with the use of UCSF Chimera software. To conduct a background search for any previously designed bladder cancer vaccines,

Vaxquery (VIOLIN, 2019) was accessed, and the amino acid and transcript accession numbers

inserted (NP\_000475.1 and NM\_000484.4 respectively). The output indicated that at that time, there were no records of any other bladder cancer vaccines in development.

	Exo 1	Exo 2	Exo 3	Exo 4	Exo 5	Exo 6	Exo 7	Exo 8	Exo 9	Exo 10	Exo 11	Exo 12	Exo 13	Exo 14	Exo 15	Exo 16	Exo 17	Exo 18	Exo 19
NM_000484.4		26170559-26170770	26111964-26112151	26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047	26000010-26000187	25997355-25997421	25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967	25905019-25905082	25897568-25897678	25891717-25891873	25880550-25881776
NM_001136131.3	26170980-26171128		26111974-26112151	26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047			25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967	25905019-25905082	25897568-25897678	25891717-25891873	25880550-25881776
NM_001136129.3		26170559-26170770		26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047			25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967	25905019-25905082	25897568-25897678	25891717-25891873	25880550-25881776
NM_001136130.3		26170559-26170770		26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047	26000010-26000187	25997355-25997421	25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967	25905019-25905082	25897568-25897678	25891717-25891873	25880550-25881776
NM_001204303.2		26170559-26170770	26111974-26112151	26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047			25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967	25905019-25905082	25897568-25897678	25891717-25891873	25880550-25881776
NM_201414.3		26170559-26170770	26111974-26112151	26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047			25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967	25905019-25905082	25897568-25897678	25891717-25891873	25880550-25881776
NM_001385253.1		26170559-26170770	26111974-26112151	26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047		25997355-25997421	25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967	25905019-25905082	25897568-25897678	25891717-25891873	25880550-25881776
NM_001204302.2		26170559-26170770	26111974-26112151	26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047	26000010-26000187		25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967		25897568-25897678	25891717-25891873	25880550-25881776
NM_201413.3		26170559-26170770	26111974-26112151	26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047	26000010-26000187		25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967	25905019-25905082	25897568-25897678	25891717-25891873	25880550-25881776
NM_001204301.2		26170559-26170770	26111974-26112151	26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047	26000010-26000187	25997355-25997421	25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967		25897568-25897678	25891717-25891873	25880550-25881776
NM_001136016.3	26140148-26140390	26111974-26112151	26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047	26000010-26000187	25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694	25911736-25911967	25905019-25905082	25897568-25897678	25891717-25891873	25880550-25881776		
XM_024452075.1	26170559-26170770	26111974-26112151	26089938-26090077	26053231-26053353	26050995-26051198	26021835-26022047	26000010-26000187	25982339-25982482	25975949-25976033	25975065-25975233	25955622-25955760	25954585-25954694							

TABLE 1: Exon sequence alignments. NCBI's Splign program was utilized to obtain all the exon positions for each of the APP transcripts.

```
>NP_000475.1 amyloid-beta precursor protein isoform a precursor [Homo sapiens]
MLPGLALLLLAAWTARALEVPTDGNAGLLAEPQIAMFCGRINMNMHVQNGKWDSDPSGKTKCIDTKEGILQYQCEVYP
ELQITNVVEANQPVTIQNWCKRGRKQCKTHPHFVI PYRCLVGEFVSDALLVPDKCKFLHQERMDVCETHLHWHTVAKE
TCSEKSTNLHDYGMLLPCGIDKFRGVEFVCCPLAEE SDNVD SADA EEDDSDVWVGADTDYADGSEDKVVEVAEEVEV
AEVEEEA DDDDEDGDEVEEEAEPEYEATER TTSIATTTTTTTSVEEVVREVCSEQAETGPCRAMISRWFVDVT
EGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAMSQSLKTTQEPLARDPVKLPPTAASPDAVDKYLETPGDENEHAH
FQKAKERLEAKHRERMSQVMREWEAEARQAKNLPKADKKA VIQHFQEKVESLEQEAANERQQLVETHMARVEAMLNDR
RRLALENYITALQAVPPRPRHVNMLKKYVRAEQDRQHTLKHFEHVRMVDPKKAAQIRSQVMTHLRVIYERMNQSLS
LLYNVPAVAEEIQEVD ELLQKEQNYSDVLANMI SEPRI SYGNDALMPSL TETKTTVELLPVNGEFLSDDLQPWHSF
GADSV PANTENEVEPVDARPAADRGLTTRPGSGLTNIKTEEI SEVKMDAEFRDSDGYEVHHQKLVFFAEDVGSNKGA I
IGLMVGGVVIATVIVITLVMLKKQYTSIHGGVVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQM QN
```

FIGURE 7: Amyloid-beta precursor protein amino acid FASTA sequence. The research database Entrez was accessed and used to obtain and confirm the amino acid sequence of APP.

### *B cell and T cell Epitopes*

B cell epitopes were predicted with the use of the database ABCpred (Suipto, 2018). The amino acid sequence NP\_000475.1 was used with a threshold setting of 0.51, window length of 16, and with the overlapping filter on. The top 10 B cell epitopes were chosen and recorded. T cell epitopes were analyzed and predicted using Vaxign which is a database that utilizes precomputed Vaxign results of over 350 genomes to calculate the efficacy of peptides in vaccine development (He et.al., 2010). This program was able to generate several epitopes of which 8 qualified as accurate and efficient.

Epitopes	MHC-1	MHC-2	Antigenicity	Allergenicity	Toxicity
LKTTQEPLARDPV KLP	+	+	Non-antigen	Non-allergen	Non-toxin
VEPVDARPAADR GLTT	+	+	Non-antigen	Non-allergen	Non-toxin
MREWEEAERQAK NLPK	+	+	Non-antigen	Allergen	Non-toxin
TTAASTPDAVDKY LET	+	+	Antigen	Allergen	Non-toxin
YEEATERTTSIATT TT	+	+	Antigen	Non-allergen	Non-toxin
DEVEEEAEEPVEE ATE	+	+	Antigen	Non-allergen	Non-toxin
VVEVDAAVTPEER HLS	+	+	Antigen	Non-allergen	Non-toxin
AADRGLTRPGS GLTN	+	+	Antigen	Non-allergen	Non-toxin
GGCGGNRNNFDT EEYC	+	+	Antigen	Non-allergen	Non-toxin
EEEEADDEDDE DGDE	+	+	Non-antigen	Non-allergen	Non-toxin

TABLE 2: ABCpred B-cell epitopes. The top ten b-cell epitopes for APP were found using ABCpred. The binding epitopes to MHC-1 and MHC-2 molecules were predicted by the IEDB database. Then the b-cell epitopes were tested for their antigenicity, allergenicity, and toxicity on VaxiJen 2.0, AllerTOP v. 2.0, and ToxinPred respectively.

### *MHC Class I and II Predictions*

The IEDB Analysis Resource (NIH, 2021) was used for the MHC class I binding predictions. IEDB uses several binding prediction methods including the Artificial Neural Network (ANN), Stabilized Matrix Method (SMM), SMM with a Peptide:MHC Binding Energy Covariance matrix (SMMPMBEC), Scoring Matrices derived from Combinatorial Peptide Libraries (Complib\_Sidney2008), Consensus, NetMHCpan, NetMHCcons, PickPocket and NetMHCstabpan. The top 10 B cell and T cell epitopes were entered in FASTA format with the default prediction method. Human was selected as the source species along with the HLA allele reference set. Peptides were sorted by predicted score. IEDB uses several binding prediction methods for MHC class II including the Consensus method, Combinatorial library, NN-align-2.3 (netMHCII-2.3), NN-align-2.2 (netMHCII-2.2), SMM-align (netMHCII-1.1), Sturniolo, NetMHCIIpan-3.1, and NetMHCIIpan-3.2. The top epitope sequences were entered along with the following settings: 1) default prediction method, 2) Human, HLA-DR as the

Epitopes	MHC-1	MHC-2	Antigenicity	Allergenicity	Toxicity
ALLLLAAWTARALEV	+	+	Non-antigen	Non-allergen	Non-Toxin
FNMLKKYVRAEQKDR	+	+	Probable Antigen	Non-allergen	Non-Toxin
MTHLRVIYERMNQSL	+	+	Non-antigen	Probable Allergen	Non-Toxin
VIYERMNQSLSLLYN	+	+	Non-antigen	Probable Allergen	Non-Toxin
MNQSLSLLYNVPVA	+	+	Probable Antigen	Non-allergen	Non-Toxin
MVGGVVIATVIVITL	+	+	Non-antigen	Non-allergen	Non-Toxin
VIATVIVITLMLKK	+	+	Non-antigen	Non-allergen	Non-Toxin
IVITLVMLKKKQYTS	+	+	Non-antigen	Non-allergen	Non-Toxin

species, 3) default length, and 4) adjusted rank for sorting.

TABLE 3: IEDB database T-cell epitopes. The top eight t-cell epitopes for APP were found using IEDB. The binding epitopes to MHC-1 and MHC-2 molecules were predicted by the IEDB database. Then the t-cell epitopes were tested for their antigenicity, allergenicity, and toxicity on VaxiJen 2.0, AllerTOP v. 2.0, and ToxinPred respectively.

### *Immunogenicity, Allergenicity, and Toxicity*

The VaxiJen database was used for the in silico screening of genomic information for immunogenicity (Doytchinova & Flower, 2007). All epitopes were entered, and "Tumour" selected as the "select target organism." VaxiJen uses tumor datasets to help predict whole protein immunogenicity with a prediction accuracy of 70 to 89% (Doytchinova & Flower, 2007). AllerTOP is a bioinformatics-based allergen prediction database that uses two primary approaches. The first approach scans peptides for sequence similarity while the second approach searches for motifs that may be probable allergens (Dimitrov & Doytchinova, 2013). In this database, the top epitopes were entered and then "Get the result" was clicked. ToxinPred is another bioinformatics tool that can be used to predict and design toxic and non-toxic peptides (Gupta et.al., 2013). Here, each of the previously generated peptides were entered with a fragment length of 10 and with an SVM (Swiss-Prot) base. An E-value cut-off of 10 was selected with a 0.0 SVM threshold. The physicochemical properties chosen to be displayed were Hydrophobicity, Hydrophaticity, Hydrophilicity, Charge, and Molecular weight.

### *Physicochemical Properties and Solubility Prediction*

The SCRATCH Protein Predictor is a tool used for the prediction of protein tertiary structures and other structural features. According to Cheng et.al. (2005), "The SCRATCH software suite includes predictors for secondary structure,

relative solvent accessibility, disordered regions, domains, disulfide bridges, single mutation stability, residue contacts versus average, individual residue contacts and tertiary structure.” All epitopes were entered with the following selected predictions: Solubility upon Overexpression, Domains, Continuous B-cell Epitopes, and Protein Antigenicity. ExPasy allows users to perform protein computational analysis to obtain several physical and chemical parameters (Wilkins et.al., 1999). Epitopes were copied and pasted into the search box and parameters computed.

IUPred was used to analyze protein disorder and binding regions. This server offers text and graphical results of these analyses including the localization of redox-sensitive regions (Mészáros et.al., 2018). All parameters were kept on the default settings (IUPred2 long disorder and ANCHOR2). PepCalc (<https://pepcalc.com/>) was used to calculate molecular weight, extinction coefficient, net charge, iso-electric point, and water solubility of the epitopes. All properties were kept on their default value.

#### *Structure Prediction*

The residues and arrangements of APP's secondary structure were analyzed using the PSIPRED 4.0 server on Prabi. Pepfold was used to predict the structure of the immunogenic epitopes and analyze them for critical energy and population-related conformations. The server

uses over 50 simulations for its analysis (Alland et.al. 2005). The Prabi/PHD secondary structure prediction server allows users to analyze and integrate secondary structure predictions (Deléage, 2017). Epitopes were analyzed with the output width of 70. The Sequence Manipulation Suite randomly shuffles a protein sequence to evaluate the significance of the sequence analysis results (Stothard, 2000). The complete FASTA sequence (NP\_000475.1) was submitted followed by the epitopes and a control group was generated.

#### *Immune Response Simulation*

C-ImmSim is a web-based immune response simulator that incorporates Miyazawa and Jernigan protein to protein potential measurements in its assessment (Rapin et.al., 2010). The complete APP protein sequence (NP\_000475.1) was entered and all parameters were kept on their default values.

## **Results**

### *B cell and T cell Epitopes*

The database ABCpred was used to scan the full length of APP for the analysis of B and T cell epitopes followed by a subsequent analysis with the use of IEDB for HLA binding affinities. The best B cell and T cell epitopes were then chosen (Tables 2 and 3). The resultant epitopes were then mapped to APP to ensure they were not found in any areas of the polypeptide chain that may be cleaved during processing (Figure 4)

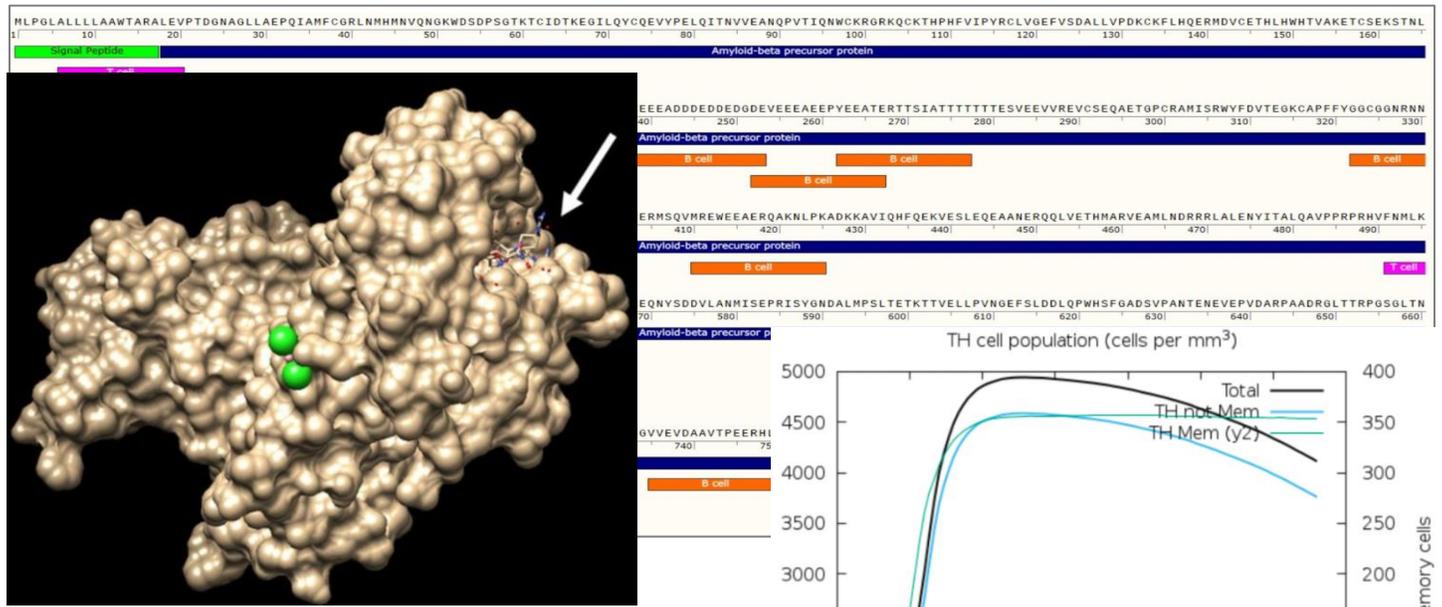


FIGURE 4: B cell and T cell epitopes. B cell and T cell epitope positions were mapped to the reference APP amino acid sequence. None were found within cleaved areas post APP processing.

### Immunogenicity, Allergenicity, and Toxicity

All B cell and T cell epitopes were rigorously tested with VaxiJen 2.0 (threshold of 0.4), AllerTOP 2.0, and ToxinPred (peptide fragment length of 10) for immunogenicity, allergenicity, and toxicity respectively. Our data show that most chosen epitopes are predicted to be good primers of the immune system (Tables 2 and 3).

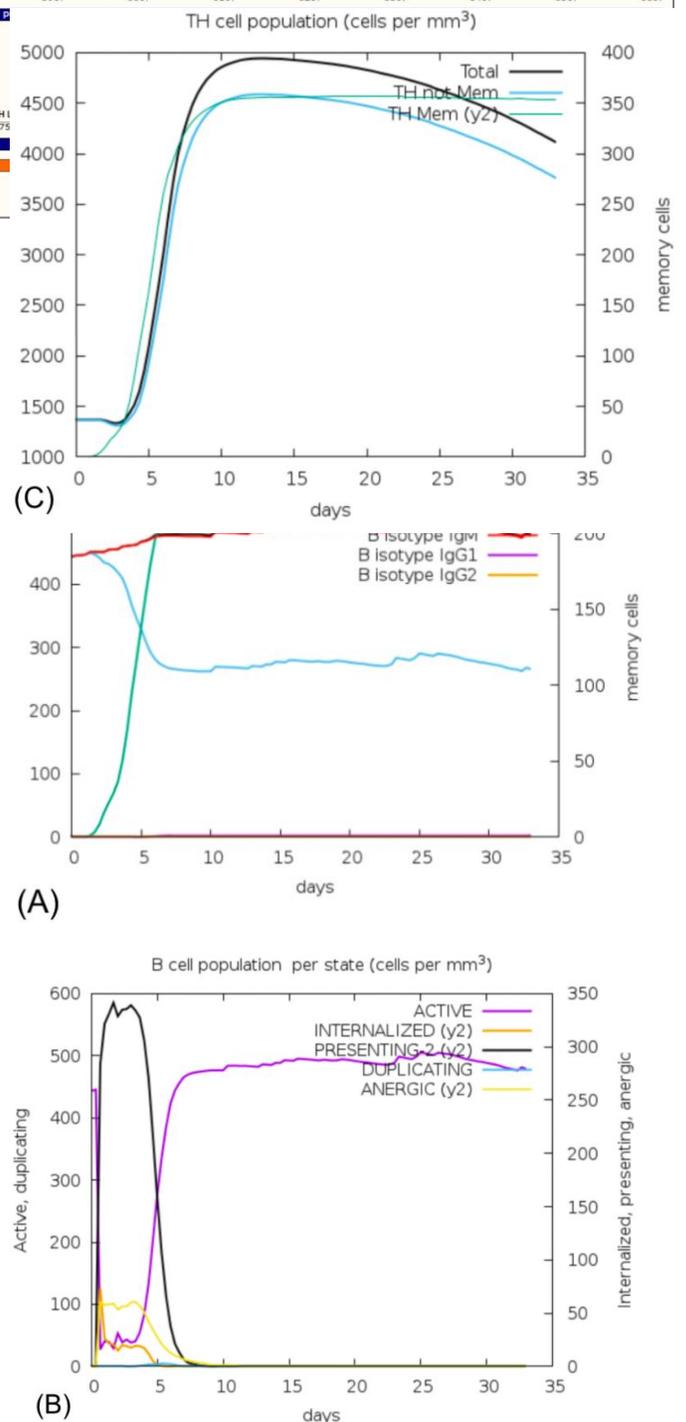
### Epitope Docking Analysis

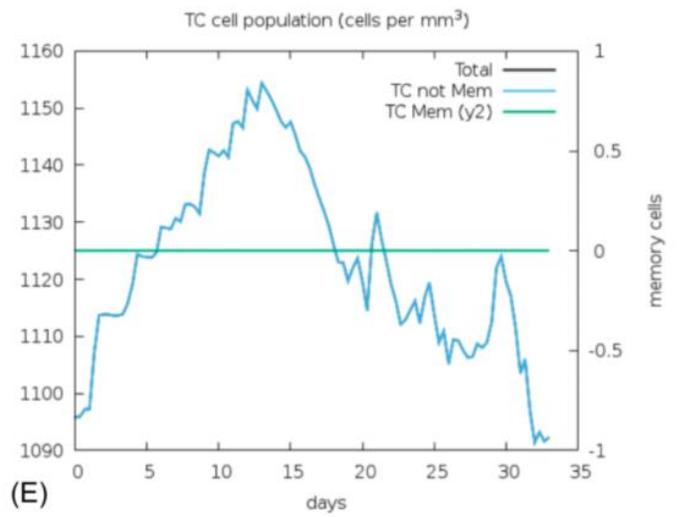
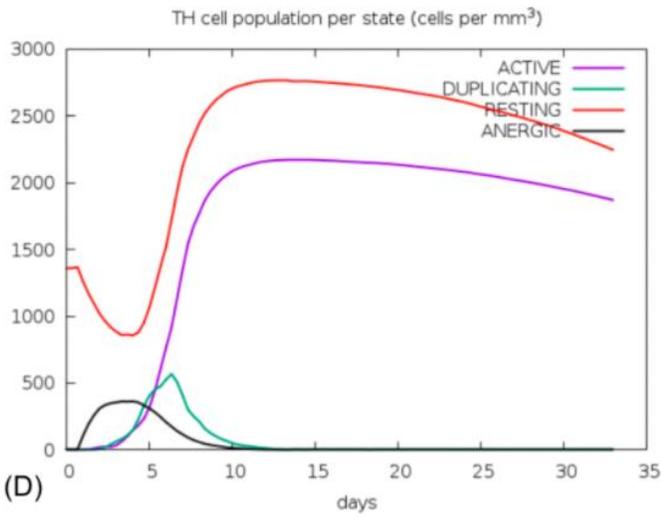
All epitopes were processed along with an HLA molecule and fitted with a docking grid to maximize affinity and accuracy. The resultant 3-dimensional structure demonstrates a good quality ligand-receptor fit predicted by in silico means (Figure 5).

FIGURE 5: Ligand docking. Simulation of HLA class I and epitope docking.

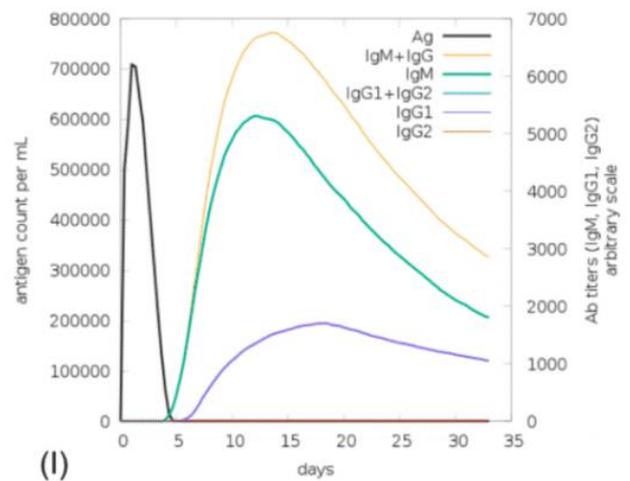
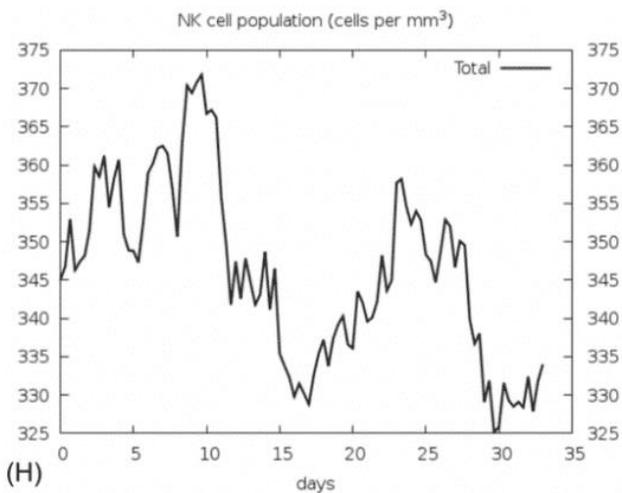
### Immune Response

The server C-ImmSim was used to model the immune response of all B cell and T cell epitopes. This simulation was conducted without the use of





an adjuvant and was processed to render an immunological study that included cell population state, lymphocyte subset, and immunoglobulins (Figure 6).



**FIGURE 6:** Immune response simulation. The C-ImmSim server was used to run a simulation of an in silico immune response of the APP vaccine. Graph description in order from top to bottom and left to right. (A) B-cell population. (B) B-cell population per state. (C) T helper (TH) cell population. (D) TH cell population per state. (E) T cytotoxic (TC) cell population. (F) TC cell population per state. (G) Macrophage (MA) cell population. (H) Natural killer (NK) cell population. (I) Immunoglobulins. This simulation revealed the production of memory B and T cells that can present the antigen and maintain a stable population throughout the challenge. These data also predicted a 15-day peak in primed cytotoxic T cells, natural killer cells, and immunoglobulins.

### Discussion

We show that bioinformatics analysis tools can be employed in the evaluation of a candidate protein as a potential antigen to be included in a vaccine. This is based on an in silico evaluation of its immunogenicity, allergenicity, and toxicity. A total of 18 B cell and T cell epitopes were rendered and demonstrated to have high immunogenicity and low allergenicity and toxicity. An immune response simulation revealed that this vaccine is likely to result in the production of memory B and T cells that can present the antigen and maintain a stable population throughout the challenge. These data also predicted a 15 day peak in primed cytotoxic T cells, natural killer cells, and immunoglobulins (Figure 6).

Previous research conducted by Jaini et.al. (2010) has determined that endogenous proteins that are overexpressed in cancer cells can be targeted with a vaccine and this can result in the prevention or treatment of breast cancer. The same methods have been employed successfully by Altuntas et.al. (2012) and Aguilar et.al. (2016). The only component that is missing here is the adjuvant that must be emulsified along with APP. In these mentioned studies, Complete Freund's Adjuvant was used which contains a subset of

over 300 proteins of *Mycobacterium tuberculosis* (Dube et.al., 2020). Since this kind of adjuvant is known to cause severe reactions when injected into humans, we propose a safer alternative, a GMP-grade adjuvant from *Saccharomyces cerevisiae*. This adjuvant has been developed and used to target various human pathogens and tumors safely and with great efficacy (Grover et.al., 2016).

One major challenge of our vaccine is that although, according to the NCBI database (2021), the human urinary bladder has a high APP expression level with a mean of 147.782 Reads Per Kilobase Million (RPKM), APP has a higher expression level (almost 400 RPKM) in the brain (Figure 3). Administering a vaccine that targets high expression levels of APP at this point might seem unsafe. However, according to Sweeney et.al. (2019), the Blood Brain Barrier (BBB) is a highly selective semipermeable border that protects the brain from toxins or pathogens that could potentially harm it. The BBB is known to filter endogenous proteins such as albumin, which consists of 609 amino acid residues and has a molecular weight of 69 kDa, while APP consists of 770 residues and has a molecular weight of 87 kDa. Although APP will be lysed into several peptides during antigen presentation, this is an intracellular event that will sensitize antigen-presenting cells to APP, but these cells will not be able to cross the BBB.

The systemic autoimmune consequences of APP vaccination must also be considered. NCBI further lists what are considered high expression levels of APP in normal adrenal glands, kidneys, and the thyroid gland of 250, 275, and 230 RPKM, respectively (Figure 3). Guo et.al. (2013) reported that gene expression levels in tumor samples are 58 times greater than that in normal samples (measured in RPKM). Taking this information into account, a targeted autoimmune response against normal cells seems less likely. According to research conducted by Aguilar et.al. (2016),

the autoimmune consequences of their developed testicular cancer vaccine were relatively benign and quite tolerable, save for the targeted attack on the tumors. This was further bolstered by Mazumder et.al. (2017) with their ovarian cancer vaccine which targeted the ubiquitously expressed receptor protein of anti-Mullerian hormone with little effect on normal cells. Although this vaccine may be useful in inhibiting the growth and metastasis of human bladder tumors expressing high levels of APP, it needs to be further investigated for possible side effects.

## Conclusion

Computational approaches may help detect epitopes with a higher degree of efficacy that are more difficult to acquire through in-vitro studies. Our results demonstrate that APP is a good candidate target protein that, if administered along with an adjuvant, can elicit a strong immune response against bladder cancer.

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# Finding ESG's Aptitude for Projecting Financial Value by Novel Machine Learning

Daniel Pyeong Kang Kim  
The Stony Brook School, USA  
thezenithcoltd@gmail.com

## Abstract

In the last few years, Environmental, social and Corporate Governance (ESG) has established its place as a measure that discloses intangible assets or liabilities of a company. Prominent as it is, there is some skepticism regarding whether ESG serves as a suitable tool for analyzing the financial prospect of an investment. While many papers concerning this metric advocate the use of ESG with their study, some claim that there are better alternatives to ESG. Thus, this paper seeks to investigate the extent by which a company's investment can be predicted with its ESG ranking, and the accuracy of ESG in doing so compared with that of other financial features. The main form of analysis used was Exploratory Data Analysis, which was employed to show any existing correlations between monetary traits. The data used for this analysis, namely the companies' financial features, was extracted from company performances in the NYSE market for the last 10 years. With 21 financial features included in each company's data, the study extracted or removed certain types of features according to their accuracy. To determine the accuracy and capability of several pipelines in classifying investments, the paper adopted eight Machine Learning Classifiers. Though these classifiers yielded similar accuracies amongst themselves, the pipelines showed a sharp distinction: algorithm classifiers containing ESG in the train process displayed a substantially higher accuracy than those without ESG. This paper demonstrates

that ESG is a comprehensive, valid instrument for investors to evaluate the accurate investment worthiness of an entity.

*Keywords: Environmental Social and Corporate Governance, machine learning,*

## Introduction

### *Background*

Receiving striking attention from contemporary analysts, ESG is an acronym that considers the environmental, social, and corporate governance aspects of a company. Since financial or income statements do not disclose the company's performance on these aspects, ESG helps to view a company's progress from a different perspective[1]. The term was first coined in the 2006 United Nations *Principles for Responsible Investment (PRI)* report. From then on, this relatively novel index facilitated the exhibition of intangible assets to the public. With the rising interest in sustainable investment, such information is becoming more invaluable to investors who desire a profound understanding of a corporation. The escalating popularity and prevalence of ESG investing have even resulted in serious discussions on placing a mandatory ESG disclosure for many companies[2].

### *Objective*

An advantage of this metric is that it is a priceless tool for investments that adhere to social responsibility. Even so, people are skeptical of

ESG's capacity to accurately reflect the monetary worth of a company. Some say it is merely a superficial report and does not represent the true financial value of an entity. It is true that the factors of ESG portray a company's ability to cope with times of turmoil[3]. Nevertheless, it may be exaggerated to claim ESG and monetary success display a causal relationship. Thus, this paper intends to display how accurately the ESG metric can determine monetary growth.

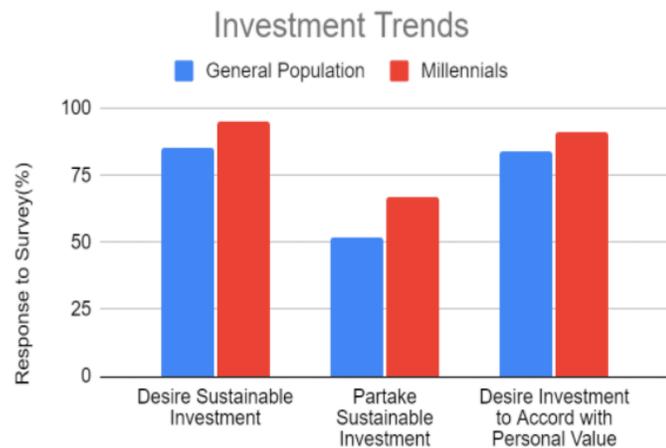


FIGURE 1. Investment trends from general population and millennials

#### Related Works

To understand other evaluations of ESG, other papers regarding the measurement were considered for general comprehension.

Having the most resemblance to this paper, attempts to display the link between ESG profiles and financial performances. The authors of the paper developed and used a sophisticated machine learning algorithm to identify the possible link. With their machine learning algorithm, the team used data from *Capitalization-weighted MSCI World Index USD* and ESG ratings from *Sustainalystics*. The final result of the study showed that though a link between the two exists, it can only be accessed with non-linear techniques[4].

Similar to the previous study, *Does Good ESG Lead to Better Financial Performances by Firms?*

*Machine Learning and Logistic Regression Models of Public Enterprises in Europe* tries to assess the accuracy of financial indicators such as ROE and ROA while identifying ESG's effect on financial performance. To calculate the accuracy of ROE and ROA, the team accessed company data from *Thomson Reuters Eikon*. The team incorporates Random Forest, Support Vector Regression, Ridge Regression, and Inferential Model to reach its objective. In the end, they concluded that ROE and ROA were accurate, which in turn supported the link of ESG with Financial performance

Unlike the two research papers mentioned above that tested the validity of ESG, *ESG2Risk: A Deep Learning Framework from ESG News to Stock Volatility Prediction* is a more specific analysis that focuses on ESG with the value volatility of a company. The main source the paper derives data from was general ESG information from news-flows. It primarily utilizes Bayesian learning and a Transformer-based language model to analyze this given data and the validity of their language model. The team discovered that the Transformer-based language model successfully predicts future volatility of stock return, thus identifying the return and the risk of a company.

Surprisingly, there was also research like *Mind the gap! Machine learning, ESG metrics and sustainable investment* that tried to replace ESG with another measurement that was more transparent and exhaustive. The team extracted data from *EURO STOXX 300* and *MSCLESG Research* to demonstrate the newly-created data's efficiency and accuracy. The paper constructs their index's validity with MATLAB built-in regression, Linear regression, CAPM, and Birr model. The final conclusion of the company was that more information could be perceived with ML techniques compared to available ESG indicators.

## Materials and Methods

### *Light Gradient Boosting Machine*

Gradient Boosting Decision Tree(GBDT), which includes XGboosting implicates the trade off problem between computation time and efficiency. Therefore, Light Gradient Boosting Machine (LGBM) solves those problems by implementing new algorithms which are Gradient Based One Side Sampling(GOSS) and Exclusive Feature Bundling(EFB). Furthermore, unlike XGboosting which undergoes level wise method, LGBM undergoes leaf wise one. GOSS first eliminates the data with low gradients and then calculates the whole information gain from the rest of the data. EFB groups the mutual exclusive variables into one bundle. An elaborately designed variable-search algorithm can produce the same thing as a histogram of individual variables by grouping them.

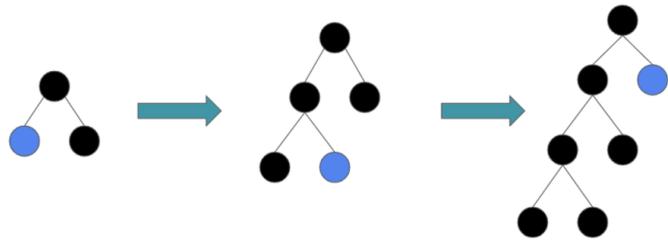
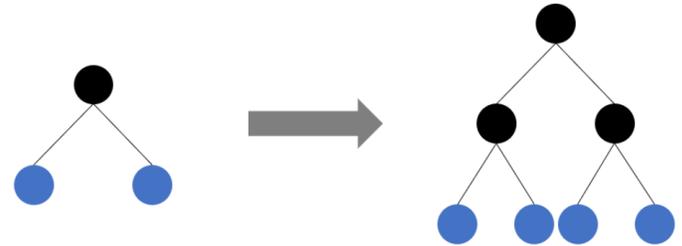


FIGURE 2. Overall architecture of light gradient boosting machine

### *Catboost*

Catboost belongs to the boosting algorithm, which focuses on handling categorical features in the given dataset. Yandex researchers developed this algorithm and it outperformed various boosting algorithms including xgboosting and gradient boosting. As the catboost performs random permutations on ordered boosting during the training process, it can prevent overfitting efficiently compared to existing boosting algorithms[]. Likewise, catboost builds a level-wise tree-like BFS algorithm, which is also suitable for the XGboosting. In order to accelerate the permutation speed, the catboost performs categorical feature combinations, which is about

bundling multiple identical features into one feature, based on the information gain. At last, lgbm or XGboosting are sensitive to the hyper parameter tuning to prevent the over fitting. However, the catboost overcomes the overfitting through the algorithms, therefore, it no longer



concentrates on hyper parameter tuning.

FIGURE 3. Overall architecture of catboost algorithm

### *Data Description*

The data used for this research, created by Immanol Recio Erquicia, is an exhaustive data that includes random investments with financial ratios and ESG ranking. Extracting information from the 10 last years of the NYSE market, the data consists of 405,258 companies with 21 financial aspects of a company including inflation, investment suitability, expected return, and ESG ranking. With the comprehensive scale of data, various pipelines were able to be devised

### *Experimental pipeline*

The accuracy of predicting whether an investment was bad or good was based on three samples: data with all features of a company excluding the ESG ranking, data where features were extracted by the correlation function, and data with exclusively the ESG ranking. The first of the three was relatively standard with Train test split and Standard scaler steps resulting in the Machine learning classifiers. The second process involved calculating the total correlation and selecting features with comparatively high correlations, which are 'inflation' and 'nominal-return'. This was followed by the usual phases of Train test split and Standard scaler. In the third pipeline, the ESG feature extracting process was added from the

first pipeline to learn the effectiveness of the ESG ranking in predicting investment suitability.

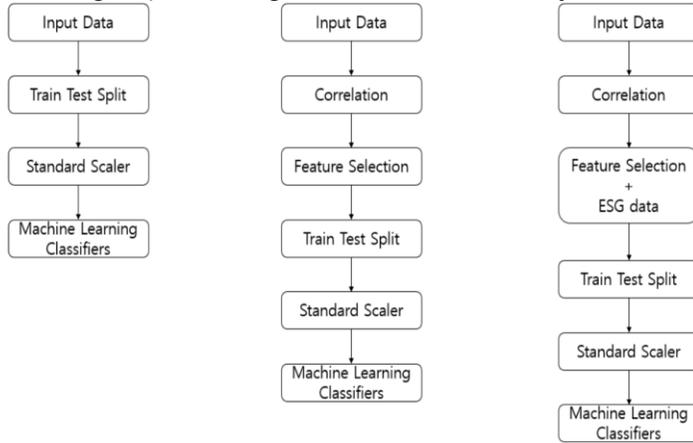


FIGURE 5. Three different experiment pipelines from our research

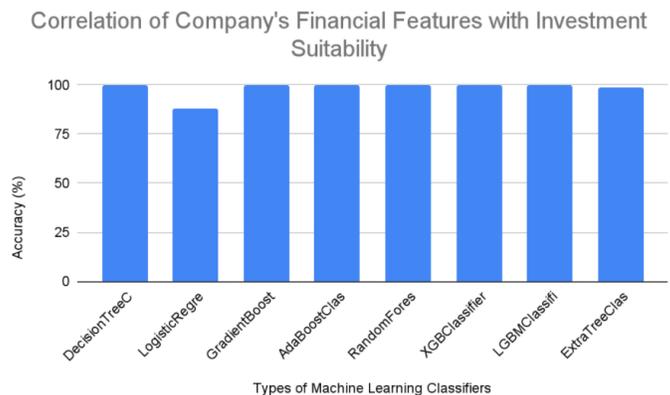
### Results

Concurring with many preceding studies on ESG's relation with financial performance, this study displays a strong relationship between ESG ranking and stock investment. To find which pipeline showed the best overall performance, this paper adopted 8 machine learning classifiers: DecisionTreeClassifier, LogisticRegression, GradientBoosting, AdaBoostClassifier, RandomForestClassifier, XGBClassifier, LGBMClassifier, and ExtraTreeClassifier. The accuracy mentioned in the experiment is how precisely each machine learning classifier was able to predict the investment suitability of a company, given its financial features.

The first pipeline, where all the features were used to identify investment adequacy, showed imposing results. The accuracy of DecisionTreeClassifier was 100, LogisticRegression was 88.06, GradientBoosting was 100, AdaBoostClassifier was 100, RandomForestClassifier was 100, XGBClassifier was 100, LGBMClassifier was 100, ExtraTreeClassifier was 99. Though there were some anomalies to how accurate the machine learning classifiers were, the overall precision was almost flawless.

Counterintuitively, the next pipeline, where three relatively higher correlations were extracted looking at the heatmap below, displayed deficient outcomes. The accuracy of DecisionTreeClassifier was 77.65, Logistic Regression was 67.37, Gradient Boosting was 76.13, AdaBoostClassifier 75.54, RandomForestClassifier was 83.2, XGBClassifier was 75.95, LGBMClassifier was 76.72, and ExtraTreeClassifier was 83.13. None of these classifiers in the second pipeline were able to yield better results than those in the first pipeline.

Outperforming the aforementioned two pipelines, the last pipeline, which used ESG ranking and the two features with the highest correlation to evaluate an investment, rendered almost flawless results. All of the machine learning classifiers except one, the logistic regression,



displayed an accuracy of 100, meaning that almost all classifiers could identify which investments were good or bad once they were given the ESG ranking of the company.

FIGURE 6. Accuracy comparison among various machine learning models based on the first pipeline

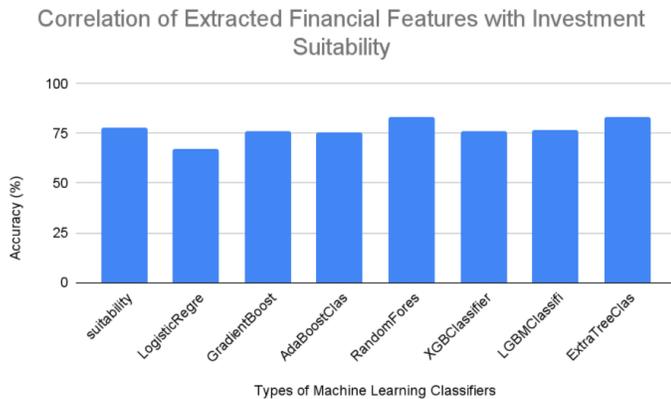


FIGURE 7. Accuracy comparison among various machine learning models based on the second pipeline

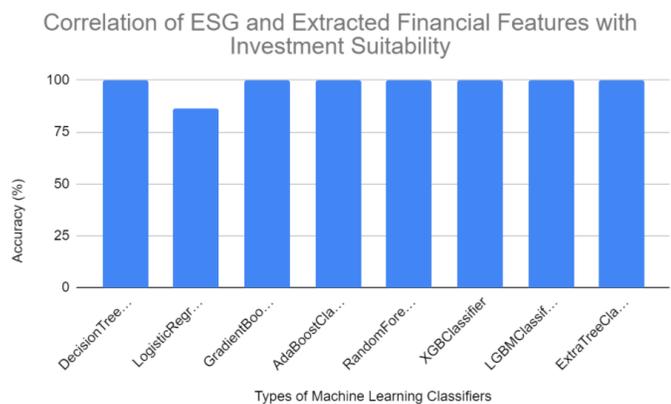


FIGURE 8. Accuracy comparison among various machine learning models based on the third pipeline

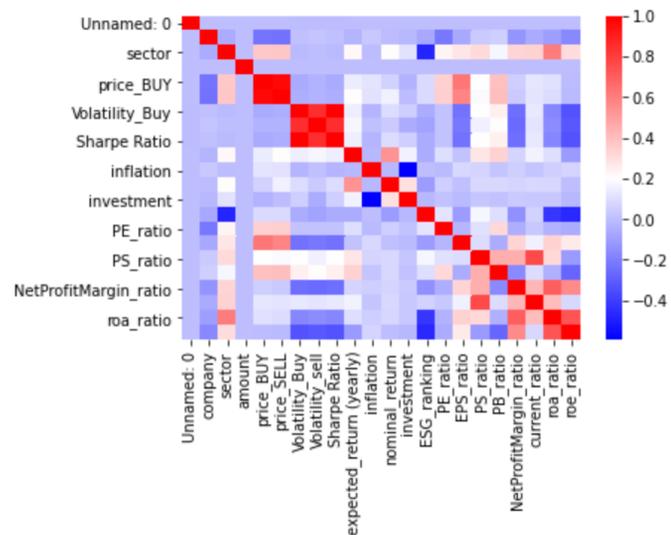


FIGURE 9. Heatmap of the correlation matrix for the feature selection

## Discussions

### Principal Finding

The most remarkable finding of our experiment was the drastic variation of accuracy in the second and third pipeline. As mentioned before, the second pipeline consists of financial features that have a high correlation relative to other financial features. As ESG ranking was not part of these extracted features, the second pipeline essentially shows the performance of machine learning algorithms without the ESG ranking. Given that the major discrepancy between the two pipelines is the ESG ranking in the train and test process, the difference in accuracy explicitly substantiates ESG's effectiveness when assessing an investment. Surprisingly, ESG seems to have a superior correlation with investment suitability than that of other conventionally employed company features such as PE or PS ratio. Unlike the previous researches mentioned in related work section, our research proved the importance of ESG variable by comparing the result through adding the ESG variable to the group of variables with high correlation result. Furthermore, our experiment discovered a limitation of feature importance function from various tree based machine learning models.

### Limitations

A major limitation of the study, though, was that the feature importance, which identifies the features that contribute the most to a certain result, of ESG was very low. Some algorithms even experienced an importance score of almost 0 for ESG, as shown in Figure 10. Nonetheless, it is implausible to assert that the high accuracy of ESG ranking with regard to investment suitability is a mere coincidence. Thus, though this result could be worrying for the advocates of ESG when viewed from a superficial level, it is logical to conclude that the low importance score is a

drawback of the feature importance itself rather than the accuracy and validity of ESG.

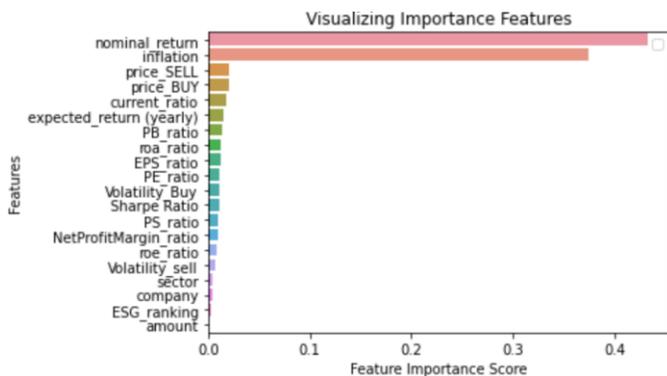


FIGURE 10. Feature importance from the light gradient boosting machine

Another limitation is the relatively low, 65 percent, accuracy rate when only the ESG ranking was used in the train and test process. This limitation shows that when investors are analyzing a company, using solely the ESG ranking will not produce the best results. Thus, we are not sure as to why classifiers with and without the ESG ranking yield stark results.

To properly find the feature and target relationship, there has to be further research by means of XAI deep learning.

## Conclusions

In short, this research paper can conclude and substantiate the utility of ESG even when analyzing a firm's financial performance.

Exploiting 8 different algorithm classifiers, the paper found a perfect correlation between ESG ranking, with two other financial features, and investment, yielding an accuracy of 100% for seven out of the eight classifiers. On the other hand, when the algorithm used train-test split for solely other financial variables, such as nominal return or PE ratio, there was a noticeable difference with accuracies ranging from high sixties to low eighties.

With the surge of interests on investment, this finding is critical for investors who are concerned with investing responsibly while making a profit. Not only does ESG represent environmental and social impact along with management structure, it also determines a company's current and future aptitude to make profit.

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**Daniel Kim**

The Stony Brook School, New York, USA

danielpkim1001@gmail.com

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# Escalating the Quantity of Medical Data Using CTGAN: Diabetes Dataset

Jihyung Kim  
jihyungkim09@gmail.com

## Abstract

The number of diabetes diagnoses is increasing sharply in the United States. It is a life-long disease that can cause serious symptoms such as blurred visions. Collecting medical data requires a consent form and goes through complicated procedures, which makes it harder. Conditional Generative Adversarial Network(CTGAN) can help to solve this problem. GAN is a Deep Learning model that manufactures synthetic data. CTGAN is basically GAN because it goes through very similar procedures, but CTGAN is for table data. We checked how accurate the fake data was to the real data using various machine learning models and deep learning. Logistic Regression(LR), Decision Tree(DT), KNN, Gradient Boosting(GB), Light Gradient Boosting Machine(LGBM), Support Vector Classifier(SVC), Gaussian, and Deep Neural Network(DNN) got 40.55%, 38.1%, 44.5%, 39%, 35.35%, 44.05%, 53.65%, 39.25%, and 34.2%, respectively. We applied GridSearch on two models: Random Forest(RF) and Light Gradient Boosting Machine(LGBM). Random Forest(RF) showed a bit better accuracy by performing 77.85% while Light Gradient Boosting Machine(LGBM) performed 76.65%. Then we decided to create a new dataset combining the fake data with a bit of real data. When we compared the new dataset with the pure real data, the accuracy scores from all models almost doubled. Although we had to modify the model in order to reach a satisfactory result, CTGAN can become a very significant model for researchers who need a large amount of data.

## Introduction

### *Background*

Diabetes is a disease caused by a lack of insulin. There are two types of diabetes. Type-1 diabetes is when the body can't produce a sufficient amount of insulin by nature. Type-2 diabetes is when the body refuses to produce insulin. Type-2 is usually caused because of being inactive or overweight(Type 2 Diabetes, 2007). Most people are not careful of diabetes because they don't notice the critical symptoms of diabetes. These are the main symptoms: extreme thirst and hunger, sudden weight loss, and tiring fatigue. And if the diabetes patient gets Diabetic Retinopathy(DR), the patient could also have vision loss(Barhum, 2019). These days, many medical companies use Artificial Intelligence software to diagnose diseases such as diabetes. Figure 1 shows how the revenue from AI is increasing exponentially, which means the usage of AI technology is increasing in the world(Statista, 2020).

### *Objective*

Medical data are very hard to collect because they need consent forms about their human rights in order to collect their data. In numerous medical research, the researchers have a hard time looking for better and more data because most of the research requires a dataset with an excessive amount of rows(Why It's so Hard for Patients to Access Their Medical Records, 2019). In order to solve the problem, we used a conditional tabular generative adversarial network (CTGAN) to duplicate and increase the data in the diabetes

dataset. Cheon et al. used CTGAN on electroencephalography(EEG) data, and could only achieve 49.8% as the highest accuracy score(Cheon et al., 2021). So we decided to use CTGAN on a diabetes dataset to see if it performs better. CTGAN first learns about the data and then makes fake data. To see if the fake data is accurate, we used seven different machine models and a default deep learning model. Our research goes in the following order: table evaluator, accuracy between the pure fake data and the original data, and accuracy between the fake data combined with original data and the original data.

### *Prior Research*

For our prior research, we found out important factors of getting diabetes using Decision Tree (DT), Random Forest (RF), K- Nearest Neighbors (KNN), Logistic Regression (LR), Gradient Boosting (GB), XG Boosting (XGB), and Catboost(CB). We used the same data as this research, and it was hard to trust the accuracy score since it had only 2000 rows. So we decided to find a way to increase the number of rows.

### *Related works*

Kevin Kuo utilized the CTGAN model to generate synthetical tabular data about the insurance dataset. Open-source R interface was used to evaluate the performance of the generated dataset, such as machine learning efficacy, distribution of variables, stability of model parameters, and it showed high ML efficacy on the insurance dataset. As the insurance data is not publicly available because of privacy issues, these results show the synthetical data of the insurance datasets made from CTGAN could be used in the future(Kuo, 2019).

Chen et al. attempted to generate text via customizable conditional text generative adversarial network. After constructing the model, they adopted an automated word-level replacement strategy in order to extract the specific keywords from the synthetic text. Lastly,

a comprehensive evaluation metric, also known as a mixed evaluation metric was applied to compare the generated one to the real one. The proposed model achieved higher performance compared to the other existing text generation models(Chen et al., 2020).

Moon et al. focus on load forecasting which is a critical issue of a smart grid. Therefore, for better prediction, machine learning and deep learning methods have been applied, but if there exists an insufficient dataset, acquiring higher performance is difficult. The research consists of two different stages. The first stage is generating the synthetic data through the various generation models including vanilla GAN, CGAN, WGANGP, CTGAN, MTD, and TVAE. In the second stage, they created the dataset based on deep learning regression models. Lastly, they analyzed the performance of the synthetic dataset through MLP, and MAPE, RMSE, MAE were used for the evaluation(Moon et al., 2020).

Seunghyun Park and Hyun-hee Park applied an oversampling and undersampling method to the network traffic data. As the network traffic mainly consists of the normal data and a minor amount of attack data, an oversampling method is essential for classifying the network traffic. They suggested a combined oversampling and undersampling method based on the slow-start(COUSS) algorithm and it outperformed the other methods including SMOTE, borderline SMOTE, adaptive synthetic sampling, and GAN by improving the F1 Scores by 8.639%, 6.858%, 5.003%, and 4.074%, respectively(Park & Park, 2020).

Cheon et al. applied CTGAN and GAN algorithms to generate the synthetic data of the EEG data. As the EEG data is difficult to gather, data augmentation is required for the BCI research. The EEG dataset was CSV format, therefore they utilized the GAN models which are suitable for the tabular data. The experiment consisted of 3

stages, in the first stage, they generated the synthetic data from each model and compared them via visualization. Then, a table evaluator function was applied to calculate the similarity score. Lastly, each generated dataset was used as input data of the various machine learning algorithms for the classification. Even though the visualization and similarity score showed CTGAN outperform TGAN, the final stage proved that there exists no significant difference between them (Cheon et al., 2021).

## Materials and Methods

### *Data description*

We used a diabetes dataset collected from Kaggle. The data are collected from the hospital in Frankfurt, Germany. Our data has 2,000 rows, which represents the number of people, and 9 columns with “Outcomes” inclusive, which represents the number of features. The features were: pregnancy term in weeks, amount of glucose in their body, their blood pressure, skin thickness, amount of insulin in their body, body mass index(BMI), diabetes pedigree function, and age. The range of pregnancy term was 17(from 0 to 17 weeks), glucose was 199(0 to 199), blood pressure was 122(0 to 122), skin thickness was 110(0-110), insulin was 744(0-744), BMI was 80.6(0 to 80.6), and Diabetes Pedigree Function was 2.34(0.08 to 2.42). The age group of the participants of the data was adults from 21 to 81(Diabetes, 2018).

### *Generative Adversarial Network (GAN)*

A generative adversarial network(GAN) is a deep learning model which generates synthetic data. GAN consists of a generator and a discriminator. The generator gets a random vector as an input and then generates the image. Discriminator discriminates against the image whether it is fake or real. The main purpose of the Generator is to maximize the probability of the Discriminator misjudging the image. On the contrary, the discriminator tries to minimize the probability of making a mistake, which leads to minimax

problems between them. However, GAN includes some downsides, which are model collapse, non-convergence, diminished gradient, and lack of a proper evaluation metric(Creswell et al., 2018).

### *CTGAN*

Lei Xu and Kalyan Veeramachaneni introduced a tabular generative adversarial network(TGAN) for applying the GAN to tabular data(XU & Veeramachaneni, 2018). However, as the tabular data consists of numerical variables and categorical variables, preprocessing both data types requires more time and memory. Therefore, a conditional tabular generative adversarial network(CTGAN) was introduced by the same researchers, to suggest better-preprocessing methods, especially for highly imbalanced categorical columns. TGAN uses a gaussian mixture model (GMM) for the training, which aims to make a distribution with a weighted sum of  $m$  Gaussian distributions. However, CTGAN utilizes a variational gaussian mixture model (VGM) instead of GMM to deal with numerical variables. CTGAN models the distribution of columns with VGM. Then, for each value, CTGAN computes the probability of each model. Lastly, it samples a mode and normalizes the value. As the TGAN implies a limitation of “class imbalance” in categorical variables, a conditional vector, loss, and “training-by-sampling” are used to solve the downside. The discrete columns usually reshape into one-hot vectors, therefore, for a more efficient preprocessing, CTGAN transfers them into mask vectors. Generator loss imposes a penalty on its loss by adding cross-entropy(Xu et al., 2019).

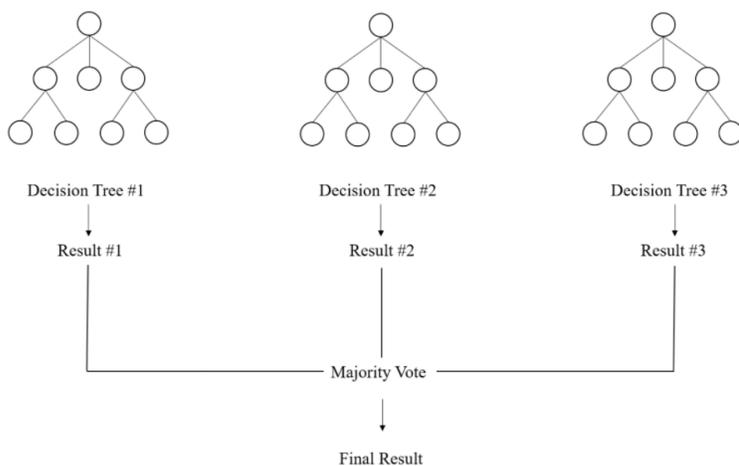
### *Random Forest*

Random forest is a representative ensemble algorithm in machine learning(Breiman, 2001). Ensemble algorithm refers to a technique that produces multiple classifiers and combines them to produce more accurate predictions. Instead of using a single powerful model, a combination of several weaker models helps predict or classify

more accurately(Dietterich, 2000). The decision tree is used as a classifier in the random forest. The bagging method is about extracting the mini dataset from the original data and then using them as input data for each classifier and also yields parallel computation. This extracting method is called bootstrapping and it allows redundancy in sampling. After each decision tree classifies the mini dataset, a final result is decided through the majority votes (Garboden, 2019).

## Results

At first, we tried to find the accuracy scores



between the fake data made by CTGAN and the default data. But as Figure 10 shows, the accuracy scores as the results were too low: Logistic Regression(LR), Decision Tree(DT), KNN, Gradient Boosting(GB), Light Gradient Boosting Machine(LGBM), Support Vector Classifier(SVC), Gaussian, and Deep Neural Network(DNN) got 40.55%, 38.1%, 44.5%, 39%, 35.35%, 44.05%, 53.65%, 39.25%, and 34.2%, respectively. So we decided to try two different ways to improve the accuracy scores. One of them was to use GridSearch to find the optimal(hyper) parameter. We used GridSearch on Random Forest(RF) and Light Gradient Boosting Machine(LGBM), and got 77.85% and 76.65%, respectively. Another method to increase the accuracy was by combining the fake data with a bit of real data. When we compared the fake data combined with a bit of real data to

the real data, Random Forest(FR) achieved the best accuracy score, getting a 100%. Other machine learning and deep learning machines also performed decent results. As Figure 11 shows, Logistic Regression(LR), Decision Tree(DT), KNN, Gradient Boosting(GB), Light Gradient Boosting Machine(LGBM), Support Vector Classifier(SVC), Gaussian, and Deep Neural Network(DNN) got 77.3%, 88.5%, 93.9%, 93.05%, 88%, 93.9%, 75.05%, and 65.8%, respectively. Figure 5, Figure 6, Figure 7, Figure 8, Figure 9 shows the comparison between the fake data combined with a bit of real data to the real data. Figure 5 shows how the mean and standard deviation between the data are almost identical exhibiting a linear line with a slope of 1. Figure 6 shows the cumulative sum of each feature. The orange lines and the blue lines each represent fake and real data, and in each graph, it is hard to see the blue(real) line because they are overlapping for most of the parts. That means they are very similar. A similar thing is happening with Figure 7, too. For the most part, each bar graphs overlap. Although there are some erratic peaks(in the graphs of pregnancies and blood pressure), the basic frames of the graphs are almost uniformed. Figure 8 shows the correlation map(heat map) of real data and fake data, and another heat map of the differences between each correlation map. The heat map that shows the differences has only a few light red colors on it, which means they are very similar. The scatter plots shown in Figure 9 are almost indistinguishable. Even the outliers are in similar locations. These figures and graphs were very helpful to understand how similar the data were.

## Discussions

### *Principal Finding*

The accuracy scores CTGAN performed were very high when we combined our fake data with a bit of the original data. Although Gan is not a popular model, researchers can use the model to increase the number of data when they lack it. Many researchers in the medical industry have a

hard time collecting valid information and data because consent forms are required in order to do so. However, modification is needed for Gan since the fake data themselves weren't as accurate.

### *Limitation*

As mentioned, the pure fake data CTGAN created wasn't as accurate. The accuracy score was only high when we combined the data with a bit of real data. Therefore, we can't say that the model itself is perfect. For our further research, we will research more about GANs and modify this problem.

### *Conclusion*

The purpose of our research is to create a synthetic diabetes dataset, in order to solve the problem of collecting medical data. We applied CTGAN to the given dataset as the format of our dataset is a CSV file. Then, we evaluated our synthetic data and real data through a table evaluator function. In addition, various machine learning and deep learning methods were used to get the accuracy score. However, the accuracy score was lower than we expected, therefore, we combined the synthetic data and real data and used them as input data. The result showed that Random Forest with Grid Search showed an accuracy score of 100 %. To sum up, even though synthetic data alone could not yield high performance, we can achieve better performance through combining the real one and the synthetic one. It showed the potential to resolve the difficulty of obtaining medical data. Therefore, for further research, we will focus on achieving higher performance by the synthetic data alone.

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# Phenylalanine Ammonia-lyase 1 (PAL1) Expression During Cold Stress in Two Japanese Tomato Varieties

Naoya Kobayashi

St. Mary's International School, Japan

naoya1221kobayashi@gmail.com

## Abstract

Cold stress is one of the most important and deleterious stresses for *Solanum lycopersicum* (tomatoes) during their growth, causing enzymatic browning, stunted growth or, in severe cases, death. *Phenylalanine Ammonia-lyase 1* (PAL1) is known to be induced during cold stress in several species of plants, but the specific role of PAL1 is still unknown. Some tomato varieties are more cold tolerant than the others, which may be in part due to PAL1 expression. In this study, our goal is to observe whether PAL1 expression varies between tomato cultivars available in Japan. Using semi-quantitative RT-PCR, PAL1 expression in both Fruitica and Momotaro cultivars was compared. The percent change between the control and treatment of both varieties was surprisingly not statistically different. The results show that both varieties are not significantly different in terms of PAL1 expression. Better understanding of cold stress tolerance genes in tomatoes can help farmers decide which varieties to buy in an ever-changing climate.

*Keywords: Cold stress in Tomatoes, Fruitica, Momotaro, Phenylalanine Ammonia-lyase 1*

## Introduction

In Japan, more than 720,000 tons of tomatoes are grown annually (Japan CROPs). Tomatoes have the best growth rate in places with direct sunlight throughout the day and prefer temperatures between 20 and 24°C. Cold stress in tomatoes is

the state where there are substantial cellular and physical changes as a result of exposure to cold temperatures. Because tomatoes are sensitive to cold temperatures, when and where tomatoes can be grown is limited. Temperatures below 15°C are too cold for tomato plants resulting in damage (Foolad and Lin, 2001). However, when temperature reach 0°C and below, the cold will kill the plant and severely damage the fruit. In January 2021, temperatures in Tokyo, Japan averaged 5.4°C, which is too low for tomatoes to grow (Japan Meteorological Agency, 2021). Even in March, temperatures in Tokyo can fall as low as 5°C.

Small modifications such as expression of various transcription factors, post-translational proteins, metabolic enzymes, and photosynthesis-related genes may play vital roles in endurance of cold stress in tomatoes (Liu et al., 2012). The taste of the tomatoes is determined by the amount of sugar, the organic acid content, and the volatile compound composition, all of which will be abnormal if the environmental temperatures are low (Mikkelsen, 2005). The cold first affects the plant at a cellular level and the problem eventually elevates when other cells die as a result. Damage to the exocarp, the outer layer of the tomato fruit, as well as discoloration of the fruit, leaves and stem tissues are consequences of cold stress, which can make the plant inedible. Both physical and cellular effects damage the plant and should be avoided at all costs.

One of the important genes for cold tolerance in tomatoes is *Phenylalanine Ammonia-lyase 1* (PAL1). PAL1 has been shown to be upregulated during cold stress in plants (Rivero et al. 2000). PAL1 synthesizes trans-cinnamic acid from L-phenylalanine; trans-cinnamic acid can become phenolic compounds which help protect against cold stress (Janas et al., 2000). In Ortega-García and Peragón (2009), PAL1 has shown to participate in the recovery process from cold stress by creating phenylpropanoids and protecting the plant from cold injury. PAL1, DPPH, flavonoid contents and total phenolic content help preserve the tomato plant at low temperatures for a long period of time (Rezaie et al., 2020). Jian-ye Chen et al. (2008) discovered that PAL1 may also play a role in heat pretreatment-induced chilling tolerance in bananas. PAL1 has many effects and supports other enzymes that maintain the health during the cold throughout several plant species. Tomatoes are a common ingredient used in many dishes throughout all seasons, but at the same time fragile and prone to bruising and from chilling injury. In order to prevent this, people have come up with solutions to grow them in winter. Many farmers often use greenhouses to make a fitting environment and grow tomatoes in them. Breeders have created tomato species that could withstand certain temperatures. The new hybrid tomatoes are stronger to cold and can withstand below 12°C while tasting the same. However, the change in expression of PAL1 in different varieties available to farmers in Japan is still unknown. The goal of this study is to compare the expression of *Phenylalanine Ammonia-lyase* during cold stress in different tomato varieties available in Japan. I hypothesize that the different tomato varieties will show different tolerance levels depending on the amount of PAL1.

## Methods

### *Plant materials and growth conditions*

The seeds of Frutica tomatoes (フルティカ) and Momotaro Fight (桃太郎 ファイト) cultivars were obtained from Amazon.com in early July 2021. They were grown for 23 days with 16 hours of sunlight at 24°C. They received 100 ml of water per pot each week. On the final day of growth, half of the plants were kept in a cold chamber for 24 hours at 4°C. Approximately 80 mg of tissue were used per biological replicate (n = 3 for each variety and treatment).

TABLE 1: RNA quality for each sample. Variety 1 was Frutica and Variety 2 was Momotaro. “C” indicates a control sample and “T” indicates a cold-stressed sample.

Sample	A260	260/280	Concentration (ng/uL)
V1T1	0.128	1.52	512
V1T2	0.141	2.47	564
V1T3	0.193	2.10	772
V1C1	0.221	2.17	884
V1C2	0.218	1.90	872
V1C3	0.202	2.20	808
V2T1	0.187	2.46	748
V2T2	0.147	2.58	588
V2T3	0.205	2.5	820
V2C1	0.093	2.52	372
V2C2	0.152	2.38	608
V2C3	0.180	2.4	720

TABLE 3: Primer sequences and amplicon sizes. Primers Tubulin-1F and Tubulin-1R are from Løvdaal and Lillo (2009).

Name	Sequence	Sequence ID	Amplicon size (base pairs)
PAL-1F	TGCGTTAAGGCTCAACAACA	SGN-U239712	200
PAL-1R	AGTTGCACAGTCACGTCTTT	SGN-U239712	200
PAL-2F	GGTAAAGACGTGACTGTGCA	SGN-U239712	204
PAL-2R	GCCAAAGACTCCAGCATTCA	SGN-U239712	204
Tubulin-1F	AACCTCCATTCAGGAGATGTTT	DQ205342	180
Tubulin-1R	TCTGCTGTAGCATCCTGGTATT	DQ205342	180

#### *RNA isolation and cDNA synthesis*

The RNA isolation process was done using the “NucleoSpin® RNA Plant” kit made by Macherey-Nagel (Catalog Takara U0120B) without liquid nitrogen for homogenization. The first strand of cDNA was made using PrimeScript 1st strand cDNA synthesis kit as described (Catalog Takara 6110A). 3.5 µg of RNA was used for cDNA synthesis. No reverse-transcriptase (no-RT) controls were also made for each of the biological samples.

#### *Semi-quantitative PCR and gel electrophoresis*

The PCR were as follows: 10 µL of EmeraldAmp MAX PCR Master Mix (Catalog #RR320A), 0.5 µL of cDNA, 0.4 µL (2µM) of both forward and reverse primers, and finally, 8.7 µL of ddH<sub>2</sub>O. Table 2 shows the given primer sequences. Primers Tubulin-1F and Tubulin-1R are taken from Løvdaal and Lillo (2009). All PCR conditions were as follows: 98°C for 2 minutes; 98°C for 15 seconds, 58°C for 30 seconds, and 72°C for 1 minute which are repeated for 30 cycles; 72°C extension for 10 minutes. PCR was done by using a miniPCR® mini16 thermal cycler (SKU: QP-1016-01). Gel electrophoresis was done by using blueGel™ electrophoresis with a built-in transilluminator (SKU: QP-1500-01).

#### *Data Analysis*

After the gel electrophoresis, the band size was quantified using Fiji (Fiji is just ImageJ) (Schindelin et al., 2012). The BioFormats plugin within Fiji was used to measure band size and peak area (Linkert et al., 2010). Finally, Microsoft Excel was used for statistical analysis and generating figures. Statistical significance was determined via one-way ANOVA. Unless otherwise indicated, “n = 3” indicates that a total of 12 samples were included in analysis (for both varieties, 3 samples each from control and cold-stressed samples).

#### **Results**

Figure 1 compares the PAL1 expression under control and cold-stressed conditions in both cultivars. As expected, our housekeeping gene, Tubulin, had a visible band in every sample, and the difference between samples was not statistically significant ( $p = 0.74$ ,  $n = 3$ ). PAL1 expression was only visible in cold-stressed samples, with an exception of one Frutica control sample. There was no statistically significant difference of PAL1 expression between the Frutica and Momotaro varieties. Furthermore, PAL1 expression was not significantly different between control and treated Frutica samples ( $p = 0.07$ ,  $n = 3$ ), nor between control and treated Momotaro samples ( $p = 0.14$ ,  $n = 3$ ).

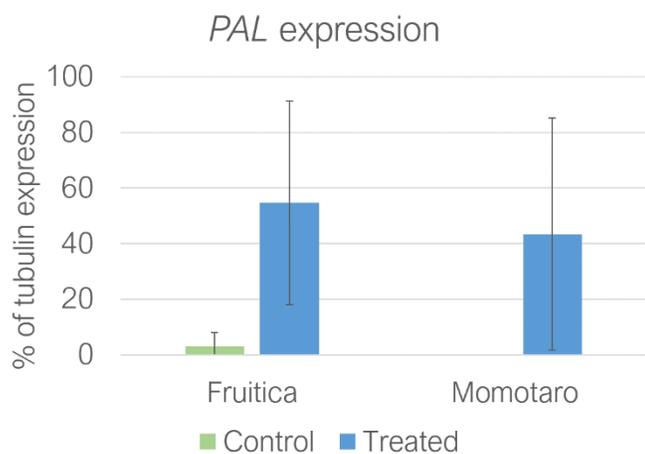


FIGURE 1: PAL1 expression in both control and treated samples of the varieties Fruitica and Momotaro.

## Discussion

Based on the semi-quantitative PCR, there were no statistically significant differences of PAL1 expression between the treated and control samples of both Fruitica and Momotaro varieties. One-way ANOVA showed that our housekeeping gene, Tubulin, also was not statically different between samples. As shown in Figure 1, the standard deviations are tremendously large, so it is not surprising that the difference between control and cold-stressed samples is not significant.

One explanation is that the duration of the cold stress was not sufficient to induce PAL1. It is also possible that the temperature was either too severe or too mild for PAL1 to be expressed. Although unlikely, the plants may not have been mature enough to express PAL1. Slight variation of the growth condition and environment, like amounts of light and water, may also affect the amount of PAL1 expression. One possible explanation for the treated sample with no PAL1 expression is that the plant died before the experiment.

There were some limitations and challenges throughout our experiment. We were unable to use liquid nitrogen for RNA isolation; however, all samples were kept on ice and lysed as quickly as possible to avoid RNA degradation.

In our PCR tests, the first set of PAL1 primers were a failure. The second set successfully amplified PAL1, but there was a secondary band likely due to genomic DNA contamination. Future work should focus on optimizing primer efficiency. Furthermore, the experiment could be more accurate with the power of qPCR.

Ultimately, we hope that this work contributes to scientists' understanding of cold stress tolerant genes, including PAL1, in Japanese tomato varieties. This information could benefit future farmers because they will be able to decide which varieties to plant depending on their climate and may give farmers peace of mind. Furthermore, better understanding of which local varieties are cold tolerant could allow farmers to extend their growing season and could even increase the rate of tomato production.

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# The Evolving U.S. Policy Toward Asylum Seekers

Inselbag Lee

St. Mark's School, United States

leeinselbag@gmail.com

## Abstract

Immigration to the United States via the southern border has proved a delicate political and legal issue throughout the years. The issue has become especially complicated given new pressures like the COVID-19 pandemic and the recent increase of illegal immigrants, especially children, at the border. The question arises as to how to reconcile international human rights for immigrants seeking asylum against the need to deter the untenable influx of illegal immigration. To untangle this question, this paper will discuss the history of immigration law and the stringent enforcement policies enacted during the Trump administration. It will also examine the difficult transition in immigrant policy since Joe Biden's election to office in 2020. The essay will then explore the international circumstances contributing to the recent immigrant surge. Ultimately, the future of immigration law requires that the Biden administration balance fulfilling campaign promises to reverse Trump-era protocols against managing the immigration spike at the southern border.

*Keywords: asylum, refugees, Customs and Border Patrol, Migrant Protection Protocols, 1951 Refugee Convention, U.S. citizenship, zero tolerance policy*

## Introduction

Seeking asylum in the United States can be a complex and arduous process, generally governed by civil procedures, but which may also have criminal implications for asylees, depending

on the circumstances of their entry. The process has grown increasingly challenging, as policy changes made during the Trump administration have resulted in stricter enforcement of immigration procedures. The matter is further complicated by a swell of anti-immigration sentiment and rhetoric bolstered by the Trump administration and former president Trump himself. The messaging and policy positions articulated by the new Biden administration purport to bode well for advocates of broad progressive immigration reform, as the administration is poised to reassess immigration policies dating back to the second Bush administration. This process will likely not be without challenges for the Biden administration, as it seeks to balance Biden's campaign promises of a more humane and equitable asylum process against the logistical and potential socioeconomic consequences of the current immigration surge at the southern border.

This essay will examine the history of the asylum process in the United States and will discuss both civil and criminal aspects of the process. Additionally, contrasting policy positions will be examined to highlight the differences between the approaches of the Obama, Trump, and Biden administrations.

## The Southern Border Surge

During the first six months of the Biden administration, unlawful entry through America's southern border reached a 20-year high (Hackman & Caldwell, 2021). The number of families intercepted by U.S. agents at the

southwestern border soared to 17,773 in February 2021, up from 6,173 in January 2021 (Jordan, 2021). Although coverage and public opinion about the recent border surge may suggest that the surge is unprecedented, such surges are a normal, cyclical part of the U.S. immigration system. Internal factors such as capacity to manage incoming migrants may impact America's ability to successfully manage incoming migrants; however, it is external, and not internal factors that typically drive such periodic surges. Conditions in asylees' countries of origin are constantly in flux, and U.S. infrastructure and policy changes may not be sufficient by themselves to create or curb an immigration surge. For example, recently drought conditions in Guatemala and economic insecurity in Central and South America heavily influence the number of individuals attempting border crossings or seeking asylum, regardless of internal U.S. policies (NPR, 2021). Massive refugee crises typically do not wait for administrations with favorable immigration policies to come into power and so the conclusion that one may draw between an administration's policies and the occurrence of a surge may be entirely illusory.

### **The Asylum Process**

In considering the U.S. asylum process, it is important to note the contextual discrepancies between U.S. policies and international norms. Under international law, an asylee may invoke asylum protection to avoid persecution in their country of origin. The United States was at least initially in agreement with this principle, as it ratified Article 31 of the 1951 Refugee Convention, which holds that a nation may not impose "penalties" upon refugees seeking asylum—even if they entered illegally—if coming directly from a territory where their lives or freedom were threatened, so long as they show good cause for their illegal entry or presence (Convention, 1951).

The U.S. is still a party to this convention, and U.S. Citizenship and Immigration Services (USCIS) policies guarantee asylees a right to a fair hearing, so long as they assert a claim within one year of entry. However, bureaucratic and political realities often impede the exercise and efficacy of this right by hindering the making of necessary claims and mandating the removal of some asylees pending their court hearing, which may prevent them from working and financially supporting their families, which may ultimately harm their asylum applications (Frum, 2019).

To better understand this process, it is helpful to examine how the nature of an asylee's entry into the U.S. affects their requests for asylum protection. The asylum process, while governed by civil laws, has potential criminal implications as well. In circumstances where an asylee has lawfully entered the U.S., they may make an affirmative declaration and application for asylum within one year of their entry. For an asylum application to be successful, the asylee must satisfy the "credible fear" standard; that is, they must sufficiently demonstrate that they are in reasonable fear of great physical harm if they return to their country of origin. If the asylum officer determines that this standard has not been satisfied, the asylee is placed in removal proceedings, which may ultimately lead to deportation, barring extenuating circumstances (American Immigration Council, 2020).

When an asylee enters the U.S. unlawfully, such as in an unlawful border crossing, a removal proceeding is initiated by the Department of Justice and the asylee may then assert an asylum claim as a defense against the removal proceedings. Prior to deportation, the asylee may obtain a hearing before an immigration judge. If the judge finds that the credible fear standard is unmet, deportation results. If the judge finds that the standard has been met, removal proceedings continue, and the asylee may present further evidence to justify the granting of asylum. In many instances, the asylee will opt to interrupt the deportation process by asserting a defensive

claim for asylum and improve the likelihood of remaining in the U.S. (Frum, 2019). It is notable that because immigration and removal proceedings are civil and not criminal, U.S. law does not provide for the appointment of counsel for asylees and potential deportees. While asylees may hire their own attorneys, they do not have the right to court-appointed counsel if they cannot otherwise afford it, thereby increasing the difficulty for many asylees to successfully present their case before the immigration court (Eagly, 2016). If an asylee is denied asylum, the decision may be appealed; however, it may take several years before the appeal is finalized and a decision is rendered.

### **Procedural Changes Under the Trump Administration**

The Trump administration made several changes to immigration enforcement and the asylum process that have made it more difficult for asylees to obtain asylum. In the pre-Trump era, asylees who had been subjected to a deportation order, but who were awaiting a final decision on their appeal, were allowed to remain in the U.S. pending resolution. Under Migration Protection Protocols (MPP), the Trump administration withdrew this allowance, mandating that all persons appealing deportation orders, including asylum seekers, be required to first return to their countries of origin (American Immigration Council, 2021). Perhaps even more stringent than the MPP was the administration's 'metering' policy, which placed a limit on the number of asylee applicants accepted at various ports of entry. If the limit was reached, any additional asylum seekers would be added to a waitlist and were sent back to their country to await a hearing on their asylum petition (Frederick, 2019). The Trump administration also instituted a zero-tolerance policy, which resulted in the separation of children from their parents at the southern border. Because of this policy, parents were often detained or deported while their children remained in the custody of Immigration and

Customs Enforcement (ICE). (Schmidt, 2019). After substantial public backlash and the failure of the federal government to reunite numerous families, the program was terminated (Rose, 2020).

It is worth noting that numerous other Draconian policies that are often attributed to the Trump administration due to its openly anti-immigrant stance and rhetoric, were in place prior to Trump's rise to power. In 2005, the Bush administration enacted Operation Streamline, which enacted the mass prosecution of undocumented immigrants. These prosecutions superseded the asylum process and prevented asylees from obtaining preliminary screening interviews with asylum officers and further limited access to legal counsel.

The absence of legal representation may have resulted in numerous asylees waiving their appellate rights by signing plea agreements offered by the government in the absence of counsel to interpret the agreements and assist asylees in making informed decisions about whether to accept them. (Schmidt, 2019). Additionally, although the Trump administration was largely blamed for the separation of families at the border, this practice began under the Obama administration as early as 2014, although the Trump administration's zero tolerance procedures exacerbated the severity of the problem (Miroff, 2020).

### **Procedural Changes Under the Trump Administration**

The Biden administration is in the process of reassessing and restructuring immigration policies and procedures enacted by the Trump administration and previous administrations. The Biden administration has come into power with significant public outcry from liberal voters to provide asylees with the full extent of their lawful protection under both international and domestic laws. The ongoing controversy over how to enforce illegal immigration laws without jeopardizing human rights may be one of the most

important topics of discourse for the new U.S. President and the American people.

Thus far, the Biden administration has made limited progress in delivering on his campaign's promises. Although Biden pledged to end the process of family separation, the practice continues, and the administration has had limited success in reuniting children separated from their parents by ICE. (The Signal, 2021). Additionally, although the administration has sought to alleviate overcrowding and supply shortages at ICE detention facilities, such problems persist (The Signal, 2021). In the wake of the Covid-19 pandemic, the Biden administration continues to expel thousands of migrant families to Mexico under Title 42 of the United States Code, Section 265, which provides for expulsion of persons who were recently in a country where a communicable disease was present. (42 U.S.C. § 265). On other fronts, the administration has been more successful. The Biden administration lifted the Trump-imposed immigration ban from Muslim-majority nations and terminated the Migration Protection Protocols program (American Immigration Council, 2021). The administration has also issued an executive order to reinstate the Deferred Action for Childhood Arrivals (DACA) program, which provides a legal pathway to citizenship for undocumented migrants who entered the U.S. as children.

A more comprehensive proposal was sent to Congress in the hopes of enacting a more permanent and enduring immigration reform act. The United States Citizenship Act of 2021 would have enacted broad reforms at every level of the immigration process and would have rolled back many of the Trump administration's immigration-restricting executive orders, creating a pathway to citizenship for roughly 11 million undocumented persons (Dickson, 2021). In February 2021, the Biden administration outlined the establishment of a task force whose responsibilities would include reunifying families separated by the Trump administration, attempting to understand the reasons for the influx of migration, and developing

a more just and humane screening process for refugees and asylum seekers (FACT SHEET, 2021). The task force will assess the impacts of the Trump administration's MPP program and will coordinate with local officials in affected countries to ensure that those on federal asylum waitlists are permitted to return to the United States pending resolution of their asylum claims, as per pre-Trump policies. This process will involve extensive coordination between the State Department, DHS, and authorities in Mexico and Central and South American countries. (FACT SHEET, 2021). In addition to assessing the policy and logistical realities of the recent immigration surge, the task force would be charged with better understanding the individual and community impacts of the immigration policies, including the experience of hardships by asylees and undocumented migrants. (FACT SHEET, 2021).

### **Barriers to Reform and the Realities of Slow Reform**

The Biden administration must carefully weigh the pros and cons of immigration reform with respect to migrants and the southern border. Currently, the U.S. is fighting the COVID-19 pandemic both from economic and public health perspectives. Biden has suggested the importance of managing expectations by stating that immigration reform will take at least a few months, if not years, to fully implement. The process will take time and not all immigration reform initiatives may be attained, especially without bipartisan support.

According to the American Immigration Council, migrants who sought asylum during the COVID-19 pandemic have been in limbo, living in tent camps along the U.S.-Mexico border without any opportunities for employment, as many are not Mexican citizens. Some have, in desperation, attempted to cross the border despite the perils and have lost their lives. Moreover, some did not even have an opportunity to plead for asylum under Trump's "metering" policy. These migrants have been told to wait in Mexico because the

“quota” for asylees had been met, denying access to the asylum process, and forcing them to wait indefinitely in Mexico. The metering policy had been used previously by the Obama administration as well during an influx of Haitian refugees in 2016. However, that metering ended in a timely fashion once “the bottleneck” had been alleviated (Murray, 2018). In contrast, the current metering policy in Mexico continued until March 2020 when processing asylum seekers at the southern border was suspended due to the COVID-19 pandemic (Leutart & Arvey, 2020).

The backlog in the processing of migrant children has raised humanitarian concerns about how long they are sheltered before being released to relatives or friends in the U.S. Another daunting issue for the Biden administration is addressing the underlying causes of immigration by confronting the instability, violence, and economic insecurity that encourages immigrants to flee from their home countries. The administration must collaborate with foreign governments and international organizations to better understand and resolve these complicated matters (FACT SHEET, 2021).

## Conclusion

The asylum process is complicated and arduous, due to the complex nature of immigration waves and surges, combined with resource and infrastructure limitations and shifting political landscape of the U.S. Although immigration surges are largely the consequence of pressures external to the U.S., presidential administrations have the power to impact the way asylees and undocumented migrants are treated during the asylum and removal processes. While this paper detailed the policies and procedures that have been enacted and repealed during the last three presidential administrations, equal, if not greater energy must be devoted to better understanding the root causes of surges in asylum petitions, as seeking those answers may improve the humanitarian response to such crises in the future. Though public opinion may lay blame

at the feet of one administration versus another, refugee crises exist regardless of the party in power. It is incumbent upon each administration to attempt to meet these crises in a manner that both seeks to alleviate the human and socioeconomic tolls that mass immigration may present, while ensuring that the human rights of all immigrants and asylees are preserved.

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# Uses of Drone & UAV Technology in Accessing Healthcare: The Case of Madagascar

Jeffrey Li  
jeffreyli7894@gmail.com

## Abstract

In the field of health logistics, drone technology has increasingly become used in delivering medical materials including blood bags, plasma, and critical pharmaceutical products to save patient lives. Among countries where existing transportation infrastructure is insufficient for the needs of hospitals and other healthcare actors, drone delivery can provide a swift and reliable solution in situations where time is of the essence. However, the present literature regarding the feasibility of UAS-supplemented healthcare logistics programs in specific nations is limited, and often restricted to wealthy and developed nations. Through a qualitative thematic analysis of factors including geography, drone capabilities, transportation regulations, and government financing, this paper finds implementing a wide-spread UAS-supplemented healthcare logistics program in Madagascar at present to be extremely difficult, largely due to stringent regulations and limited government funding. Despite these challenges, future implementation is not impossible, as some steps can be taken towards resolving them, given that government interest in the uses of drone technology grows overtime.

*Key words: UAV, UAS, Drone Health Logistics, Madagascar, Feasibility*

## Key Terms and Distinctions

Drone - A commonly used term to describe any unmanned aerial vehicle which can travel autonomously or beyond a visual line of sight, including those that can travel in water or on land.

UAV - Abbreviation for Unmanned Aerial Vehicle. It refers to drones that travel through the air, specifically, the traveling vehicle component. All UAVs are drones, but not all drones are UAVs. However, for this paper, the two terms will often be used interchangeably.

UAS - Abbreviation for Unmanned Aerial System. It refers to all the parts which enable UAVs to function properly, including the ground control unit (the *controller/remote*), *GPS*, and the *UAV itself*.

## Introduction

### *Aim*

This research paper aims to investigate factors affecting the implementation of a UAS-supplemented healthcare logistics program in rural Madagascar and provide recommendations for its creation through a themed analysis. It must be noted that this paper is limited and best understood as an introductory analysis into a complex area. This paper does not explore in-depth the financial feasibility of such an operation, but rather, broadly explores the multitude of components affecting possible implementation.

### Objectives:

1. Identify and summarize existing relevant literature on drone usage for medical & logistical purposes and best practices in the field
2. Distinguish tangible benefits, disadvantages, and critical factors necessary to determine the feasibility of such a drone healthcare logistics program

3. Investigate the needs and priorities of Madagascar's healthcare system, as well as the capacity of Madagascar to implement such a program.
4. Provide a list of the next steps administrative bodies in Madagascar may take to make the implementation of such a program easier.

### *Background*

Globally, the usage and applications of drone and unmanned aerial vehicle technologies have substantially grown over the past two decades. At present, there is a growing demand and market for drone technology in the delivery of medical products including vaccines, blood supplies, and general pharmaceutical products (Euchi, 2021). According to Global Market Insights (2019), in 2018, the entirety of the medical drone market was valued at USD 88.2 million and is projected to grow to about USD 399 million by 2025. Proponents of UAV technology in medical logistics often cite cost-savings, versatility, and swift delivery speeds as benefits to its implementation in health systems.

Under the COVID-19 pandemic, interest and exploration in this field's potential have grown significantly from health providers and private corporations alike. With successful UAV-logistics companies like Zipline operating in Rwanda, various local and national governments in sub-Saharan Africa have identified this technology as a potential area of development in their respective health systems.

In addition, the growth of medical logistic industries in all forms aids in attaining the 3rd and 17th United Nations Sustainable Development Goals regarding "Good Health & Well-Being" and "Partnership for the Goals" (United Nations, 2015):

3.8 Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.

3.3: By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.

17.17: encourage and promote effective public, public-private and civil society partnerships, building on the experience and resourcing strategies of partnerships

Madagascar is an African island country located in the Indian Ocean, off the southeastern coast of the African mainland. With a population nearing 27 million people as of 2019 and a land area of 567,000km<sup>2</sup>, Madagascar has a GDP of \$14 billion and is classified as a 'low-income country' by the World Bank (2021; n.d.). Under the United Nations Human Development Index (HDI) rating system, Madagascar ranks 164th out of 189 nations with a 0.528 rating, which is both lower and growing slower than its southeast African counterparts (Kenya - 0.601, Zimbabwe - 0.571) (UN, 2020).

The top health priorities of Madagascar are related to infectious diseases, malnutrition, human resources deficiency, limited funding, and limited access to healthcare (Barmania, 2015). In 2018, there were 233 incidences of tuberculosis per 100,000 people and 76.1 incidences of malaria per 1,000 people at risk (World Health Organization [WHO], n.d.).

### **Methodology**

The methodology used for this project primarily involves a literature review through sources such as academic papers & journals, news articles, and relevant Madagascan legislation found through databases such as JSTOR, Google queries, and official government websites. Although the drone industry's fast-paced development has led certain information to become outdated fairly quickly, I found date-restricting certain queries for topics such as medical drone delivery literature in Madagascar greatly limited both the quantity and quality of research I could obtain on the topic. However, the vast majority of referenced sources are still relevant and created within the past five years.

Some keywords used in my queries include 'medical drone delivery', 'Madagascar drone regulations', 'UAS', 'UAV', and 'Health Logistics'. To guide the direction of my research, I had also conducted two informal unstructured interviews with experts in the field of drone technology, one of whom is Mr. Lei Zhang, founder, and CEO of the drone-logistics company Antwork Technology based in Hangzhou, China. To a considerable extent, this paper takes a qualitative approach, using thematic analysis to identify critical factors and form conclusions.

## Discussion

### *Public Health - Accessibility*

From high Karst-landscape plateaus running down the middle of the island to thick tropical forests lining the coast, Madagascar contains many biomes and varying topographic features (World Wide Life, n.d.). Unfortunately, the roads in this varied, vast, and rough terrain are "scarce or of poor quality." For certain rural areas, even with access to vehicular transportation, arranging a trip would be costly and difficult. Movement across this terrain "requires creativity and innovative partnerships, often with those in other sectors, such as conservationists" (Barmania, 2015).

A significant portion of Madagascar's population lives in what their national statistics bureau classifies as rural areas, and in 2019, the percentage of people living in rural areas in the country accounted for 62% of its total population (Macrotrends, n.d.). With 16 million Madagascans living 5 kilometers or further from a health center (USAID, n.d.), and the only widely available public transportation being bush taxis or taxi-bes (taxi cars or vans used for both short and long-distance travel) between relatively large Madagascan cities or towns, transportation options are limited for those living in more remote or hard-to-reach areas (Hoffman, 2014). In addition, the cost of transportation can be a significant and often unconsidered barrier to healthcare access (Shrime et al., 2017). This is one reason why healthcare utilization in

Madagascar remains low, with a rate of only 30% of the population seeking government-funded healthcare services for fever (Marks et al, 2016). Moreover, a severe shortage and geographic inequality of trained medical professionals exists between rural and urban areas. Technical specialist Felix Andrianjaranasolo explains how at most, a town in Antananarivo would have "12 doctors but in more remote areas, there is often only one health-care professional and often not even a doctor, maybe just a midwife" (Barmania, 2015).

Drones can bypass the constraints imposed by the physical geography and limited infrastructure by simply flying over them. In the event of a natural disaster, where geographic features are significantly altered, drones appear to be a natural solution to moving vital equipment and essential medical goods on-site rapidly. In areas with little access to the road network or rural communities with few trained medical professionals, drones can deliver all the same and encourage the development of alternative digital solutions to physically visiting a doctor. Drones could also reduce the cost of logistics, as multiple drones can be piloted by one pilot or control center simultaneously.

### *Public Health - Healthcare Costs and Funding*

Healthcare is mostly free of charge in Madagascar, with some expenses being paid for out-of-pocket by patients. Although healthcare is provided by the government, the sector is funded from a mix of sources, with public tax only funding 47.7% of the total expenditure in 2016 (WHO, 2016).

A quarter of Madagascar's total health expenditure is paid for by external sources such as non-governmental health organizations, programs like USAID, or donation programs. However, this heavy reliance on foreign aid has proven to be a vulnerability in the country's ability to fund its healthcare program.

In 2009, a political crisis led to a coup of the national government by the then-mayor of Antananarivo, Andry Rajoelina. Governmental

instability severely affected Madagascar's ability to fund its healthcare:

The 2009 political crisis had a substantial impact on the country's health sector, from budget cuts to donor withdrawal. Jean-Claude Mubalama, a health specialist at UNICEF, said: 'It's clear that since the crisis, the budget allocated to the health sector has decreased.' This shortfall, he explained, had a bearing on the ground with the departure from rural areas of many health-care workers who had not been paid. Some left to work for non-governmental organizations, others headed to the capital Antananarivo in search of work (Barmania, 2015).

Due to the fallout of the 2009 crisis on the healthcare sector, healthcare had turned into a national priority for all governments since. It must be acknowledged that the quote cited above comes from an article written in 2015, and since then, the budget allocation has started to increase again.

The 2020 Madagascan budget for healthcare saw an increase of 26% from the previous year, jumping from Ar 546.8 billion (USD 144 million) to Ar 688.9 billion (USD 181 million) (UNICEF, 2020). The upwards trend in Madagascar's health budget allows more potential funding for the creation of a drone logistics pilot program. However, until such a program reaches maturity and widespread application, instability in the nation's governmental institutions could cause foreign donors to once again withdraw their aid and limit funding for lower-priority and experimental healthcare initiatives.

#### *Technology - Technical Limitations*

There are three critical aspects when considering drones purposed for delivery. They are range, load, and speed. Differentiating between custom-designed and commercially available drones is also crucial.

The undisputed global industry leader in drone manufacturing is the Shenzhen DJI Technology Corporation, holding a solid 76% market share in the US alone, despite trade-war tariffs specifically targeting Chinese drone companies (Schroth,

2021). Their longest range commercially available drone is the Mavic Air 2, "with a transmission distance of up to 10 km" (DJI, 2020).

While conventional drones often use four blades connecting to a central frame, certain companies like Zipline have designed drones similar in appearance and function to gliders to maximize range. Zipline's winged drones have "a top speed of 128 km/hr, and a round trip range of 160 km, carrying up to 1.75 kg of cargo" (McCall, 2019). In Australia's Northern Territory, which covers a vast terrain, researchers from Charles Darwin University and iMOVE (a leading applied research center in Australia) are hoping to develop drones with a range of 250 km in all weather conditions (iMOVE, n.d.).

Traditionally, progress in the drone logistics industry has been hampered by technical limitations and insufficient capabilities. Increasingly, however, innovative advancements in the three critical aspects are progressing exponentially. With sufficient funding and by learning from these advancements, more companies, organizations, and governments can create drones capable of conducting long-distance deliveries.

#### *Technology - Weather*

Drone operations may be particularly ill-suited for Madagascar's east coast weather during the rainy season. Throughout the year, tropical cyclones formed from the trade winds of the Indian Ocean slam into the Island's east coast, partially causing the high average annual precipitation of coastal regions, which vary" from 2,030 mm to 3,250 mm" (World Weather & Climate Information, n.d.). On average, Madagascar faces 1.5 cyclones annually (UN OCHA, 2019).

Madagascar enjoys a tropical and temperate climate, with most regions including Antananarivo having minimum temperatures of around 10°C in the coldest months, and highs of around 30°C in the warmest months (Yu Media Group, n.d.).

While Madagascar's temperature would not pose a problem for drone operations, as most drones feature a temperature operating range between

0°C and 40°C, the strong winds and heavy rain could affect operations during hurricanes and the rainy season in coastal areas of the country (Spires, 2019).

### *National Regulations and Laws*

National laws on drone usage remain stringent and inflexible. Madagascar does not differentiate between commercial and personal drone usage and will not allow anyone to fly a drone outdoors without a specialized permit (Dronemade, n.d.; Jones, 2017). From 2016-2018, the State University of New York (SUNY) at Stony Brook operated “the ‘DrOTS: Drones Observed Therapy System in Remote Madagascar’ project [as] a proof-of-concept” in “deploy[ing] healthcare in remote settings”. One of the biggest problems they encountered related to regulations: “the lack of drone-specific flight regulations led to delayed flight permit approval and required frequent renewals thereof” (Knoblauch et al, 2019).

After reading the relevant laws, it becomes evident that there are severe limitations in one’s ability to operate a drone and a significant number of bureaucratic processes required to obtain the special permit.

In Madagascan legislation, under Article 3 of the section, ‘Relative aux conditions d’exploitation des aéronefs télépilotés’ (Relating to the operating conditions of remotely piloted aircraft), drones are not allowed to fly through clouds and fog; less than 30 meters away from vehicles, buildings, boats, or people for drones weighing 4 kilograms or less; more than 50 meters above the ground for drones weighing more than 4 kilograms; and cannot surpass a speed of 80km/hour at full power—to name a few restrictions (Aviation Civile de Madagascar [ACM], 2015a).

The permits given to fly drones are also on a case-by-case basis and only valid given a pre-approved flight plan, meaning it will only be useful for one flight. Up to 20 additional documents are required to apply for the permit alone (ACM, 2015b).

The current controls on drone operation in Madagascar largely negate the potential benefits

of drones as a logistics tool. Namely, access, flexibility, and speed. For private drone technology corporations looking for business opportunities in the country, the regulations are very clearly red tape obstacles that could discourage investment and access into the market. The requirement for a pre-approved flight plan restricts flexibility and limits sudden changes to the scheduled route due to weather or problems arising from the ground. The limitations on UAV speed and the lengthy bureaucratic process required to receive a permit take away the benefit of quick delivery in both emergency and non-emergency situations. As of the present, the largest obstacle to implementing a drone logistics program for any industry or field in Madagascar would be its uncompromising legal framework.

### *Case Studies - Antwork Technology*

Antwork Technology is a drone delivery logistics company headquartered in Hangzhou, China. It was the first company in China to receive a license from the Civil Aviation Administration of China (CAAC) for urban drone deliveries and has carried out 50,000+ drone flights since its inception in 2015 (UAS Vision, 2019; LinkedIn, n.d.). Through an informal interview over the internet with the company’s CEO & Founder Mr. Zhang, several critical considerations were brought up regarding the roles both national governments and intergovernmental organizations play in creating balanced regulations which ensure civil safety and encourage economic development.

Mr. Zhang explains that China is a member state of the Joint Authorities for Rulemaking on Unmanned Systems (JARUS), a “group of experts gathering regulatory expertise from all around the world” with “63 countries and the European Aviation Safety Agency (EASA) and EUROCONTROL [contributing] to the development of JARUS work products (JARUS, n.d.)”. He says the CAAC created new standardized regulations based on the Specific Operations Risk Assessment (SORA)

methodology developed by JARUS, taking advantage of the already present expertise in the field and applying it in specific UAV and UAS applications. SORA is a 10-step process that holistically assesses the risks of drone operations in detail.

He also mentions how in response to Antwork being licensed for urban drone delivery, the Hangzhou municipal government set up a pilot zone for unmanned aviation in coordination with the CAAC (Zhejiang Government Site, 2020). This provided a space for real-world testing, finetuning urban drone delivery, and learning about any unexpected challenges resulting from such operations.

While Hangzhou's pilot program is primarily designed for testing urban UAV flights, there is also no shortage of examples where pilot zones have been opened in rural settings in sub-Saharan Africa as well, starting with UNICEF's Malawian drone corridor set up in 2017 (UNICEF, 2017).

At present, Madagascar is not a member of JARUS and has not taken the initiative to create a designated area for UAV technology testing outside of a case-by-case basis with a select few research institutions.

#### *Case Studies - Rwanda & Zipline*

Perhaps the most successful and well-known example of a drone logistics company operating in sub-Saharan Africa is Zipline. As of early 2021, Zipline had already flown 4 million miles, making over 400,000 vaccine, plasma, and blood deliveries across countries like Rwanda, Ghana, and the United States under contract with both national and local governments (Boudway, 2021). By 2019, the company was delivering "more than 65 percent of Rwanda's blood supply outside of the capital, Kigali" and "[increased] the use of rare and specialized blood products by 175 percent and reducing waste and spoilage by over 95 percent" in the country as compared to 2016 figures (McNabb, 2019).

This example in particular also highlights the benefits UAV technology has over the physical

terrains of nations. Rwanda is known as the 'land of 1000 hills,' and "[the] maintenance costs of the country's roads are very high as the roads get destroyed due to heavy rainfall and landslides. Even if they try to maintain the roads, their budget does not allow them to do so" (Gangwal et al., 2019). UAVs, however, can bypass the logistical challenges of rough hills, blocked roads, and traffic conditions.

While Zipline's commercial success is remarkable, in Rwanda's case, its government had enlisted more than just Zipline in its bid to become the technological and financial hub of Africa. In 2020, the government hosted the first African Drone Forum in Kigali, inviting international regulators and companies alike to learn from and participate in a series of UAS delivery competitions on Lake Kivu (African Drone Forum, 2020). By hosting the first forum of its type in the region, Rwanda established itself as a leader for technological innovation and business in Africa. Rwanda is also one of only four African members in JARUS (JARUS, n.d.).

The public-private partnership between Zipline and Rwanda tangibly illustrates a successful example in Africa which Madagascar could seek to emulate, should their aviation regulators choose to pursue future drone and UAV logistic operations in the medical field.

#### **Conclusions**

This research aimed to identify and determine factors that may affect the success of implementing a medical drone logistics program in rural Madagascar. Based on the broad analysis of topics in public health, technology, and regulations, any large-scale UAV operations in Madagascar within the near future will be unlikely and difficult.

The technological and public health discussion provides both the means and the reasons to implement a UAV program, and case studies have shown successful examples of real-world applications in environments similar to rural Madagascar's. However, strict regulations and

bureaucratic redundancies remain as large obstacles to all extensive drone operations.

Nonetheless, there still are several clear steps Madagascar can take to improve the likelihood of future development in its drone industry. Most critically, amendments to the current legislation regarding drone laws will be required. While balancing the interests of corporations and both environmental & personal safety can be difficult, an easy step towards resolving this issue would be to join JARUS and seek advice from other experienced aviation regulators and adopt the SORA methodology to streamline and standardize risk assessment procedures. As every nation has different circumstances, the solutions every nation requires will be different. Therefore, pilot programs or testing areas could provide valuable practical information about cost and operational feasibility for the optimal solution for Madagascar.

To make comprehensive and necessary changes to current laws, input from more than just the local aviation administration will be required. Of the most relevant governmental bodies to this topic, the Ministère de la Santé Publique (Ministry of Public Health), Ministère des Transports, du Tourisme et de la Météorologie (Ministry of Transport, Tourism, and Meteorology) and the Aviation Civile de Madagascar (Madagascar Civil Aviation Administration) could form an interministerial committee to resolve concerns about regulations from all angles.

The drone industry is rapidly developing in various fields on every continent. Though Madagascar lacks the necessary framework to handle larger drone operations, I am confident that as time passes, the benefits of UAV technology and its applications will be better understood and valued by the country's government and prompt action for its use.

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# Memories Slipping Away: My Grandmother and Dementia

Grace Molano

Pioneer Valley Chinese Immersion Charter School, United States

gamo9663@gmail.com

"Who is that?" My grandma asks as I come into view on the phone screen.

"That's Grace, your granddaughter," my mom says. "She's the tall one. Remember?"

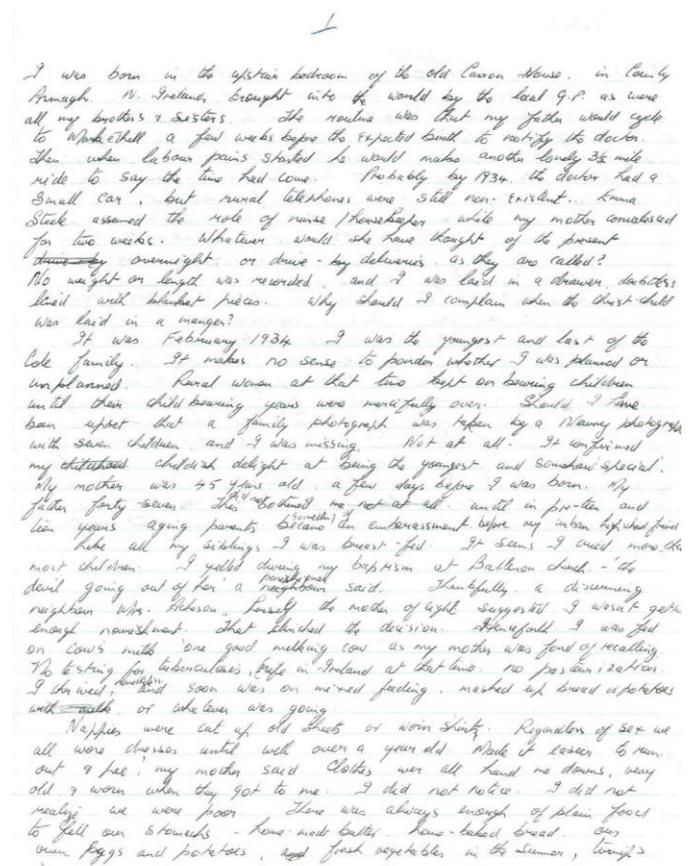
"Hi Grandma!" I say leaning over the back of our couch to wave at the camera.

"Oh, hello," my grandma says with a hint of an Irish accent. I cannot tell if she remembers me.

My grandmother, Doris, was born in 1934 in rural Northern Ireland. At the time of her birth her father had to bike three and a half miles to alert the doctor, since they had no car or telephone. She spent the first couple months of her life in a drawer cushioned by blanket pieces.

As a kid she spent her time exploring the small farm that her family owned and played with dolls made of sticks. She attended school at a small schoolhouse down the road. There were only a couple rooms, so she learned alongside children of many different ages. As the Germans became a concern the students brought gas masks to school in fear of bombs. During her school years she fell in love with books and read voraciously. When she turned eleven, she was chosen to take a scholarship exam. She had one of the top scores in the country on this exam and was given a scholarship to grammar school. Because of this opportunity she was able to complete an accelerated medical school program and do her residency in the United States, where she met my grandfather.

Now, at eighty-seven, my grandma has dementia, and many of these memories would have been lost if she had not written them down.



I was born in the upstairs bedroom of the old Carron House, in County Antrim, N. Ireland, brought into the world by the last 9 P.M. as were all my brothers & sisters. The routine was that my father would cycle to Monkethell a few weeks before the expected birth to notify the doctor. Then when labour pains started he would make another lonely 3 1/2 mile ride to say the time had come. Probably by 1934, the doctor had a small car, but rural telephones were still non-existent. Anna Steele assumed the role of nurse (housekeeper) while my mother convalesced for two weeks. Whatever would she have thought of the present ~~stagnant~~ overnight or drive-by deliveries, as they are called? No weight or length was recorded, and I was laid in a drawer, cushioned with blanket pieces. Why should I complain when the best child was laid in a manger?

It was February 1934. I was the youngest and last of the Cole family. It makes no sense to ponder whether I was planned or unplanned. Rural women at that time kept on bearing children until their child-bearing years were miraculously over. Should I have been upset that a family photograph was taken by a Navy photographer with seven children and I was missing. Not at all. It compensated my childhood childhood delight at being the youngest and somehow special. My mother was 45 years old a few days before I was born. My father forty-seven. She ~~retained~~ retained no pot at all until in five-teen and ten years aging parents ~~became~~ became an embarrassment before my in-laws by their first like all my siblings I was breast-fed. It seems I cried more than most children. I yelled during my baptism at Ballinacree, the devil going out of her a Protestant neighbour said. Thankfully, a discerning neighbour Mrs. Gibson, formerly the mother of eight suggested I wasn't getting enough nourishment that I should be given. Thankfully I was fed on cow's milk, one good thing, low as my mother was fond of recalling. No looking for lactulase, safe in Ireland at that time. No position, no view. I arrived, and soon was on mixed feeding, mashed up sweet potatoes with ~~with~~ or whatever was going.

Vegetables were cut up, all sorts of warm soups. Regardless of sex we all wore dresses until well over a year old. Made it easier to run out of pee, my mother said. Clothes were all hand no downs, very old & worn when they got to me. I did not notice. I did not realize we were poor. There was always enough of plain food to fill our stomachs - home-made butter, home-baked bread, our own eggs and potatoes, and fresh vegetables in the summer, turnips.

FIGURE 1: A page from the memories my grandma wrote down

My grandma has seen the world change drastically. She began her life with no electricity or car. As a child she lived through World War II. As

an adult she was an anesthesiologist at Mass General Hospital and raised a family. Now she is living through the pandemic. However, dementia has taken many of these memories from her. She often forgets about the pandemic and wonders why we cannot visit more often, or why we have to wear masks around her. She even forgets that she is in her own home and will ask my grandfather to take her home.

“John,” she will say looking over to my grandfather, “will you drive us home?”

“Oh yes, let me find my keys,” my grandfather will respond, not remembering that his license was revoked years ago.

“You already are home,” someone will say. She gets confused when the whole extended family is visiting because it is outside of her normal routine, and she thinks that she is at one of our houses.

We have to find humor in these moments because without it watching their memories deteriorate would be too unbearable.

My grandma can no longer recall many of the details of her own life, but she routinely asks about her seven siblings.

“How is Lorry doing?” She will ask my mom. As we are sitting in the living room with her gathered around her wheelchair. A cup of fresh tea in her hand.

“He died years ago, you went to his funeral,” my mom will respond.

“And Bea?” Grandma will ask.

“She’s dead too, you’re the last one.”

Dementia means that my grandparents can no longer live independently. They have a team of home health aides who provide round the clock care. My aunt and her family have moved back into their house to provide additional care that is needed. My grandma needs help dressing and getting into her wheelchair. She no longer does any cooking or cleaning.

My cousin has been reading to our grandma, which is something she still enjoys, but it can also lead to confusion. She is known to say “we have to leave” or “let my people go” during conversation since she has been reading Bible

stories. She will also talk at length about the journey she and my cousin took across the Oregon Trail after he read Oregon Trail by Francis Parkman to her.

Hearing these things brings on a mix of emotions. It is hard to see that my grandma remembers so little about who she is, but she seems happy with these memories, and I am glad that she is happy remembering them even though they are not real.

She will also often repeat questions, forgetting that she had just asked.

During my little sister’s eighth birthday party we had parked my grandma’s wheelchair in the grass in her yard, so she could be a part of the celebration. My grandma asked me multiple times about how my sister’s biological grandparents were so young. Whenever she noticed the baby in a playpen grandma would ask who she was, and I would re-explain that that is my sister’s aunt, her grandparent’s kid.

It can be hard to have the patience for such circular conversations, but I know that it must be harder for my grandmother to not be able to remember things like this.

Dementia is the reason my grandma has lost so much of herself. Dementia is a general term for an impaired ability to remember, think, and make decisions. More than 55 million people worldwide suffer from dementia (“Dementia”, 2021). There are five common types of dementia: vascular dementia, Alzheimer’s disease, Lewy body dementia, frontotemporal dementia, and mixed dementia. There are also reversible causes of dementia (“What is Dementia?”, 2019). We do not know what type of dementia my grandma, though we do know it is probably not vascular dementia. It can be hard to determine the exact type of dementia patients have because the symptoms and brain changes of different dementias can overlap (“What is Dementia?”, n.d.). My grandma probably has Alzheimer’s because it is the most common type of dementia.

There are many factors that can contribute to someone getting dementia. However, there is not a good understanding environmental and non-

genetic risk factors for dementia because studies often have conflicting results. Women are more likely to have Alzheimer's than men, which may in part be due to hormonal factors and estrogen. In men poor education can be a risk factor for Alzheimer's. Further studies are being done to see if this is education during childhood, or life-time acquisition of knowledge. Chemical exposure, and specifically aluminum exposure, may be a risk factor for Alzheimer's. Having an old or young mother is also a risk factor for dementia. (McCullagh, 2001). There is also evidence that in the UK the prevalence of dementia in African-Caribbean people is higher than that of White people. This suggests that ethnicity and race may be a risk factor for dementia. It is hypothesized that this is because there may be a difference in environmental risk factors between these two groups of people. (Adelman, 2011).

In the DSM-5 dementia is categorized as a Neurocognitive Disorder. This is further divided into major and minor Neurocognitive Disorders. The criteria for a minor Neurocognitive Disorder includes evidence of moderate cognitive decline, and neurocognitive decline in formal testing. However, the person is still able to function independently. Major Neurocognitive Disorder is characterized by evidence of significant cognitive decline, and the inability to live independently ("Diagnostic Criteria for Dementia", n.d.).

Dementia patients are also likely to have complications such as pneumonia, febrile episodes, and eating problems. These complications are frequent with advanced dementia and are associated with high six-month mortality rates. These patients also often have distressing symptoms such as labored breathing and pain. There are also likely to undergo burdensome intervention in the last three-months of life. It can be discouraging to think that these things might happen to my grandmother, but patients whose health care proxies understand the prognosis of dementia are less likely to undergo burdensome procedures at the end of their life (Mitchel et al, 2009). I hope that knowing

this will help to prevent my grandma and others with dementia from having burdensome procedures at the end of their lives.

When someone has dementia beta-amyloid proteins clump together to form plaques that collect between neurons. This disrupts the neurons' ability to function, as they can not send signals to other neurons, which can impact memory, behavior, and many other things. Additionally, a protein called tau will bind to itself forming tangles inside neurons. Normally tau binds to microtubules which are structures that help guide nutrients and other molecules from the cell body of the neuron to the axon and dendrites. When tau forms these tangles it blocks the neuron's transport system which makes communication between neurons harder. Also, neurons will be injured and die which breaks down the neural network and the neuron's ability to communicate with other neurons ("What Happens to the Brain in Alzheimer's Disease?", 2017).

There is currently no cure for Alzheimer's, but patients can do treatments that help alleviate symptoms. For example, there are some medications that can help Alzheimer's patients with memory and cognition ("Treatments", n.d.). To help my grandma we try to give her activities that will keep her brain stimulated. This could be reading a book to her, having her do a puzzle, or having her attend events at the senior center. This has become more challenging with the Covid-19 pandemic, as it is not very safe to take her places even though she is vaccinated.

Caring for a person with dementia can be difficult. Informal caregivers often experience burnout. Factors that are associated with caregiver burnout are extensive informal care provided by the caregiver, and a decreased quality of life for the caregiver. Reduced cognition, decreased quality of life, and severe neuropsychiatric symptoms and depression in the person with dementia are also associated with informal caregiver burnout (Lethin et al, 2018).

My aunt is an informal caregiver for my grandparents. She puts a lot of work into taking care of them, and it can be a stressful job. However, my family is lucky enough to be able to have home health aids go to my grandparents' house every day to help my aunt take care of them. I can imagine that for families who do not have that privilege the burnout and stress that they experience must be much greater.

It can be hard watching my grandma live with this disease. There are many doctor's appointments and occasionally hospital visits, but the hardest part is seeing her loss of independence and cognitive skills. She now struggles with having a simple conversation which is a stark contrast to the doctor she used to be. I take comfort in the fact that she seems happy. She no longer has the stress of cooking and cleaning when family comes over. She loves having so many people there to take care of her. She is happy that she can live in her house with her husband instead of in a nursing home and her happiness is the most important thing.

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## My Grandparents' Battle Against COVID-19

Julia Moosikasuwana

Manhasset Secondary School, United States

julia.moosikasuwana@gmail.com

"This Chinese broccoli is so expensive," my grandmother complained, snaking through aisles of fruits and vegetables amid hordes. On March 19, 2020, my grandparents scavenged multiple Chinese supermarkets to stock up on groceries, preparing for a deadly scourge befalling the city. My grandfather inspected various fish nestled in open beds of shaved ice. Their cart was laden with many ingredients planned for culinary delights: garlicky shrimp in soy sauce; crispy, fried whiting; and sauteed snap peas with tender slivers of pork or chicken.

At home, they cooked dinner to the noise of the Chinese television. My grandmother's serene but concentrated face focused on washing and chopping meat and vegetables, while my grandfather's hands maneuvered the fiery, cast iron wok. Because their senior center would close soon due to a mysterious virus, they pondered their uncertain future of self-imposed home isolation and frequent cooking.

Two days later, my grandfather developed a dry cough and a low-grade fever. When he told my grandmother, her eyes widened with the realization that they had neglected to wear masks at the supermarkets. Worried that my grandfather contracted COVID-19, my mother, a general internist, advised him to take hydroxychloroquine and azithromycin--unapproved treatments at the time. Upon hearing of my grandfather's symptoms, I was terrified, but my mother comforted me, advising that the medications could help. My grandfather started these medicines reluctantly but still felt ill.

To my family's dismay, my grandfather continued to cough and feel weak. At the local urgent care center, the doctor wielded long, thin probes to sample mucus inside my grandfather and grandmother's noses. This COVID-19 polymerase chain reaction (PCR) test detects the ribonucleic acid (RNA) of the SARS-CoV-2 virus. My grandmother's test took four days to return negative, while my grandfather's test took seven days to return positive.

Using a pulse oximeter device that my mother foraged after phoning eight pharmacies, my grandmother and grandfather's oxygen saturations were initially 94% and 97%, respectively. The next day, 92% and 97%. On Saturday, Grandpa's X-ray of his lungs had white patches, revealing pneumonia. COVID-19-induced pneumonia has a tendency to affect both lungs. They become filled with fluid and inflamed, limiting one's ability to take in oxygen and causing shortness of breath, cough, and other symptoms. Pneumonia associated with COVID-19 can be especially severe and result in breathing difficulties that take months to improve. Moreover, my grandfather's oxygen saturation fell dangerously low to 91% that day, so his doctor referred my grandfather to the hospital for further evaluation--two weeks after their shopping trip. My grandparents had always seemed invincible. They grew up in the rugged farmlands of rural China and met while working long hours at a food market in Venezuela. Because of their limited English proficiency, my grandmother sewed clothes in the sweatshops of Chinatown, and my grandfather picked up passengers in his yellow

cab late at night into the morning. Awed by their courage and countless sacrifices, I never imagined that they could face near death due to an invisible pathogen.

My grandmother helped my grandfather pack his toiletries for his trip to the hospital. His medicines, his shoes, and his slippers fit neatly into his bags. At the front of the emergency room doors, my grandmother was stopped by hospital staff wearing surgical masks, isolation gowns, gloves, and face shields. They asked who the patient was, and upon hearing her answer; they sent my grandmother away. Because it was too dangerous for her to enter the emergency room, she waved farewell with downcast eyes, unsure if she would ever see him alive again.

Soon after my grandfather was admitted to the hospital, my grandmother fell ill. She developed diarrhea and took medicine for it. She lost her taste of food, so she no longer enjoyed her favorite dishes. Like my grandfather, she developed a low-grade fever. Despite taking Tylenol, she still felt lethargic and dizzy, so she laid all day in bed.

One day, she suddenly lost track of her slipper. Its disappearance puzzled her. Alone in her house, she left her bed and walked to the kitchen, and her eyes widened. All of the empty takeout boxes that had piled up on the table had fallen to the ground, and under the wreckage was her lost slipper. When did all of these boxes fall? she wondered, for surely, she would have remembered hearing the crash of the plastic containers. She then realized that she was unable to remember yesterday's events. She frantically called her eldest daughter, distraught that she had lost her memory.

My aunt insisted that my grandmother go to the hospital and arranged for my mother to take her there later that night. In the emergency room, Grandma noticed that there were very few people there, and there were many empty beds. The onslaught of the pandemic was only starting for the unsuspecting hospital staff. Upon occupying

a bed, Grandma was questioned about Grandpa, who was staying at the same hospital.

Unbeknownst to our family, Grandma had developed life-threatening, severe hyponatremia due to diarrhea, poor oral intake, and her blood pressure medication, so they started giving her intravenous saline through an IV catheter. Her doctors wanted to admit her to the medical intensive care unit for closer monitoring as they corrected her hyponatremia, but the unit was full. When inpatient treatment corrects sodium levels too quickly, a patient can develop osmotic demyelination syndrome, a form of brain damage. Symptoms may manifest for several days after a sodium overcorrection, and can include impaired speech or swallowing, limb weakness, seizures, confusion or depressed consciousness. In the most severe cases of pontine myolysis, one can develop locked-in syndrome. The damage and dysfunction can be permanent.

Upon hearing the mention of the IV catheter, I recalled the dreaded shots I received annually. The singular moment that the needle pierced my arm was painful, and having an IV catheter in my hand for hours was inconceivable. However, I relaxed when I learned that it was a plastic tube that my grandmother could barely feel. Three to four hours passed before the nurse returned, saying that the bag of intravenous saline fluid was finished. Grandma felt relieved, until the nurse said, "Now we need to give you another bag of water." Grandma asked, "Of what?" and the nurse replied, "Of sugar."

Hours later, Grandma was brought into a very small room without a bathroom. Morning approached, and Grandma's bed was brought to sit up so that she could eat the breakfast perched on her lap. She became thirsty and called someone in her room for water. Later, she rang the bell again, and upon arriving, her nurse told Grandma that everytime the nurse entered the room posed a great risk for the nurse. The nurse asked Grandma to request everything at one time. Grandma was surprised, but she recalled that the nurse wore two pairs of gloves, a plastic

isolation gown, three masks--an N95 respirator and two surgical masks, and gloves and that her nurse needed to change her personal protective equipment after each visit to her room. My grandmother apologized and began to call her nurse much less frequently.

A room became available later in the day, and my grandmother exited her small cubicle and moved into a large room on the eighth floor. My grandfather had been living on the sixth floor. Armed with this knowledge, my grandmother ventured out into the hallway in search of an elevator that would take her to her husband. She looked around curiously in the hallway, eyes scanning for the familiar number of my grandfather's room, when a staff member stopped her. "What are you doing?" they questioned. She told them she was looking for her husband. "You can't leave your room. It's dangerous," they reprimanded, sending her back to the eighth floor, dejected. My mother suggested that my grandmother ask to be in the same room as my grandfather, but my grandfather informed her that his room was already fully occupied with other patients. The doctors allowed my grandfather to see my grandmother, but my grandfather lacked the energy and strength at the time, for the coronavirus had robbed him of his usual vigor and enthusiasm.

However, one day, at 3 o'clock in the morning, my grandmother heard people bringing someone to her room. Why does that look like my husband? she wondered. It was Grandpa! Three people had helped him pack up everything in record time and moved him into her room. My mother informed me that many people were dying in the hospital of COVID-19. "I am glad that you are here," she said, and he returned her sentiment. They ate and conversed as if they were at their own dining table at home until they finally fell asleep.

Due to hospital visitor restrictions, I could only FaceTime them at the same time. I listened to their comments about their living conditions. "The food at the hospital is very good," my grandfather

stated joyfully. I thought of his particular gastronomical tastes and wondered how the hospital meals compared to the five-star family recipes that my grandmother and he taught my mother and me. My cousins and I conversed about their news and our worries. At night, when our grandparents fell asleep in their hospital beds, we would lie awake, making promises to the stars and pleading for our grandparents' safety.

My grandmother longed to wash her hair, but she was apprehensive about falling because of her dizziness. "I'll be right outside of the curtain," my grandfather assured her. "If you fall, I'll be here to rescue you."

When it became clear that my grandfather was developing respiratory failure, the doctor prescribed high doses of dexamethasone medication to reduce inflammation and Anakinra, an interleukin-1 receptor antagonist and an experimental treatment for COVID-19. My grandmother's health was improving, but Grandpa remained very ill. His oxygen saturation was measured to be 92%, so he received supplemental oxygen by nasal cannula continuously and slept in the prone position for better oxygenation. His doctor instructed my grandfather to walk from his bed to the window and back for exercise. His oxygen saturation was measured after his exercise to be 92%, and my grandma's oxygen saturation was 97%. Over time, my grandfather's oxygen requirements gradually increased, and my mother informed me that he would need to be placed on a ventilator soon. His breathing had become so labored that his loud voice was reduced to a whisper metered by his respirations.

They fell into a routine quickly. Each day, a phlebotomist would visit their room and take their blood four or five times, maybe even more. The skillful workers would draw it more easily, but clumsier ones would miss the vein completely, so needle holes dotted my grandparents' hands. As my grandmother told me about this procedure, I winced, scolding my mind for conjuring up gruesome mental images. I found a yearly blood

draw detestable already, and I was unable to imagine experiencing it multiple times per day. Furthermore, two bags of saline solution and one bag of sugar solution would flow into my grandmother's veins frequently, and my grandmother took three or four sodium pills a day. On the fifth day, my grandmother agreed to be discharged, for that day, she felt that her dizziness had subsided. They stated that she could return home tonight, so she packed up her belongings and removed the IV catheter from her hand. Then, they drew her blood. Her doctors noticed that her sodium levels were dropping again, and they delayed her discharge. "We will need to give you another bag of saline solution." My grandmother casually said that she removed her IV catheter by herself. "What?" they exclaimed, shocked. "How could you do that by yourself?" She was surprised at their sternness. They inserted another IV catheter, and after three hours, the bag of saline solution was empty. Her doctors provided her with a prescription, and a wheelchair whisked my grandmother to the lobby. A woman assisted my grandmother in bringing down the belongings to my mother, who left my grandfather a bag of oranges and plums before driving my grandmother home.

The daily blood tests showed that the levels of his inflammatory markers were decreasing, and his oxygenation was improving. His oxygen requirements decreased, which signified that his lungs were healing and that his immune system was adequately controlling the virus. However, he lost 15 pounds in 15 days in the hospital. Weight loss occurs because the body must expend tremendous energy to upregulate important functions, such as increased cardiac activity, oxygenation of damaged lungs, and increased immunologic activities.

Although my grandparents are very old, I almost lost both of them within a short time frame of two weeks during a pandemic. I learned that we are never prepared to lose our loved ones, and that miracles can happen. After many months, my grandmother's sense of taste was restored, so

she could enjoy her culinary dishes again. However, long after my grandparents' recovery, they still suffer some long-lasting effects of the coronavirus: Their speech has become less energetic and less smooth. They possess only half of their usual energy, and their breaths are short and shallow--symptoms of a phenomenon termed long COVID. Long COVID has many other names: long-haul COVID, post-acute COVID-19, long-term effects of COVID, or chronic COVID.

Moreover, their memory has deteriorated. My grandmother, who once joked about losing her memory and mistaking me for my cousin, forgets pieces of information more easily. Her sharp mind, which was once able to compute long multiplication in seconds or critically eye a piece of cloth that she fed her sewing machine, has also worsened, and she finds it more difficult to focus. Nevertheless, despite their side-effects, I feel inspired by their amazing survival.

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## “Natalie is a late bloomer”

Cocoro Motoyoshi

The Greenwich Country Day School, United States

cmotoyoshi22@gmail.com

There was a teenage girl named Natalie living in Rural America, U.S.A. Her hair was blonde and her body was as small as a 5 year old. She lived in a one-bedroom apartment as the youngest of 10 siblings. Natalie got low grades in school and was bullied for her size. Every day when she came back home from school, she would sob for hours until her eyes got swollen. During the chaotic time of the Covid-19 pandemic, Natalie's wealthy classmates were talking about how they see the doctor through telemedicine in order to stay safe and healthy.<sup>1</sup> Natalie had to borrow the neighbor's computer because in her financial situation she could not afford a digital device. Classmates that did not have digital devices could not go to the doctor at all to prevent the risk of being infected with Covid-19.<sup>2</sup> During that time, the U.S. was going through a massive decline of in-person doctor's visits.<sup>3</sup>

Natalie's miserable life with mean classmates at school had become a normality, and her daily life seemed to be unchanged and dull. The one thing she had not realized was that she had been drinking a jug size amount of water everyday. One day Natalie's mother, Dianne, noticed Natalie drinking excessive amounts of water, so her mom decided to take her to the doctor's office in far away Urban City. One early morning, it took three hours for Natalie and Dianne to travel by walking and riding a crowded bus to the doctor's office.<sup>4</sup> After an hour, the wealthy looking doctor told Natalie and Dianne that she

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<sup>1</sup> Wealthy people have the luxury of having digital devices, so they can receive healthcare while social distancing. Digital devices are more difficult to obtain for people with lower socio-economic backgrounds. According to this article, 46% have used telemedicine, but the remaining 54% have not. The 46 % that used telemedicine had a higher median household income than patients that didn't use telemedicine. Armaun Rouhi, "Disparities in access to telemedical care during the pandemic," published on July 31, 2020, <https://penntoday.upenn.edu/news/disparities-access-telemedical-care-during-pandemic>

<sup>2</sup> Remote Technology made a huge impact on the healthcare industry during the times of Covid-19. Remote Technology was a way to provide healthcare while maintaining hygiene. Remote technology is a way to slow down the spread of Covid-19. Karthikeyan Iyengar, "Learning opportunities from Covid-19 and future effects on health care system," published on June 20, 2020, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7305503/>

<sup>3</sup> The decline of in-person doctor's visits is greater than other types of healthcare visits. The Covid-19 pandemic urged many Americans to stay home, and avoid going to the doctor's office in-person as much as possible. Ateev Mehrotra, "The Impact of the Covid-19 Pandemic on Outpatient Visits: A Rebound Emerges," published on May 19, 2020, <https://www.commonwealthfund.org/publications/2020/apr/impact-covid-19-outpatient-visits>

<sup>4</sup> Currently, people in Rural America have the inconvenience of driving long hours to go to the doctor's office. The lack of patients at rural hospitals tends to lead to pay cuts of healthcare providers. Austin Price, "The lasting impact of the Covid-19 pandemic on our healthcare delivery system," published on May 4, 2020, <https://news.berkeley.edu/2020/05/04/the-lasting-impact-of-the-covid-19-pandemic-on-our-healthcare-delivery-system/>

has Type 2 diabetes. Dianne was so scared and worried because the family could not afford medication for ongoing diabetes treatment. Natalie's family did not have health insurance.<sup>5</sup> After many thoughts, Natalie and Dianne decided to receive metformin.

Metformin is a drug that's used for people with Type 2 Diabetes. It is a drug that controls the blood sugar level of Type 2 diabetes patients. Metformin is usually used with a combination of other medications, diet, and exercise.<sup>6</sup>

In order to receive metformin, Dianne created a GoFundMe page pleading for people's sympathy for a little sick girl. Dianne worked hard by asking her friends to donate for her little girl and calling the principal of Natalie's school, to ask the entire school community to consider giving donations for receiving metformin. Dianne did not sleep to work hard in order to meet the donation goal. In the beginning, there was no donation on the GoFundMe page for a while. Later on, Natalie gradually received donations to the GoFundMe page from friends, teachers, and classmates. Dianne luckily received enough donation funding in order to purchase metformin.

10 years later, Natalie became an activist politician that focuses on healthcare policy. Because Natalie experienced the Covid-19 pandemic, she realized that making healthcare more affordable is necessary even after the pandemic ended.<sup>7</sup> She developed and pushed policies of healthcare reform in order to provide more federal funding to hospitals to avoid the lack of hospital beds that almost ended her young life.<sup>8 9</sup>

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<sup>5</sup> \*In America, we are living in the reality where many of our citizens aren't able to afford health insurance. 8 million Americans create Go-Fund me sites to receive donations, in order to pay for healthcare. Another 12 million Americans create funding pages to help friends pay for healthcare. David U. Himmelstein, "The U.S. Health Care System on the Eve of the Covid-19 Epidemic: A Summary of Recent Evidence on Its Impaired Performance," published on Jun 30, 2020, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7331107/>

<sup>6</sup> <https://www.webmd.com/drugs/2/drug-11285-7061/metformin-oral/metformin-oral/details>

<sup>7</sup>In U.S politics, healthcare is a topic that's being brought up frequently. Many politicians bring up health care accessibility within their campaigns. Healthcare workers have recalled that the temporary Covid-19 funds won't help the healthcare industry in the long-term. Lauren Weber, "Hollowed-Out Public Health System Faces More Cuts Amid Virus," published on July 1, 2020, <https://khn.org/news/us-public-health-system-underfunded-under-threat-faces-more-cuts-amid-covid-pandemic/>

<sup>8</sup> Healthcare reform is not only important during tragic events like the Covid-19, it's important to think about healthcare reform for the long run. Early actions play a critical role on how Covid-19 is being spread. Kim Krisberg, "US public health meets Covid-19 head-on: Pandemic squeezes long-underfunded public health system," published on May, 2020, <https://www.thenationshealth.org/content/50/3/1.1>

<sup>9</sup> National leadership is necessary in order to avoid a healthcare burnout. Funding in local and state departments is necessary for a robust healthcare system. Doctors and healthcare workers can't solve this healthcare issue by themselves. Charles B. Holmes, "How Lessons from Global Health Can Improve Health And The Response to Covid-19 In The US," published on August 10, 2020, <https://www.healthaffairs.org/doi/10.1377/hblog20200806.949101/full/>

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# Characterization of Lupeol, Linalool, and Squalene Synthase Expression Within Floral, Leaf, and Seed Tissues of *Camellia japonica* and *Camellia sasanqua*

Katherine O'Shea

The American School in Japan, Japan  
koshea2003@gmail.com

## Abstract

*Camellia japonica* (tsubaki) and *Camellia sasanqua* (sazanka) seed oils are both marketed as tsubaki oil, a traditional Japanese beauty product applied to the hair and face. However, differences in cosmeceutical benefits between *C. sasanqua* and *C. japonica* oils are not yet fully understood. Here we aim to characterize differences in expression of antioxidant-synthesizing enzymes between the *sasanqua* and tsubaki species of *Camellia*. Using semi-quantitative RT-PCR, we compared gene expression of linalool synthase, squalene synthase, and lupeol synthase from *Camellia* seeds, petals, and leaves. *C. japonica* had a greater expression of linalool synthase in seeds relative to *C. sasanqua*. Within *C. japonica*, linalool expression was greater in leaves than in seeds. Due to the challenges of degenerate primer design, primer efficiency varied for each of the three genes studied. Nevertheless, the results suggest there is a difference in expression, and possibly a difference in antioxidant profiles, between the two species commonly used for tsubaki oil. Better understanding the concentrations of secondary metabolites between species and tissues could lead to improving the quality and efficiency of *C. japonica* and *C. sasanqua* oils as cosmeceuticals.

## Introduction

*Camellia japonica* oil, or tsubaki oil (椿油) in Japanese, is the natural oil made by cold-pressing the seeds of a *C. japonica* plant, has been used in Japan and other East Asian countries since ancient times. It saw a particular rise in popularity during the Edo period (1603-1868) when it became commonly used for hair grooming. It is often used as a moisturizer for skin and hair because of its sebum like composition (Jung et al., 2007), which allows it to penetrate multiple layers of skin while retaining moisture. Tsubaki oil is also noted to have a high content of oleic acid, a fatty acid that stimulates hair growth and has anti-inflammatory properties (Keis et al., 2007). While tsubaki oil popularity has died down a little since the Edo period, there are still a few big companies that continue to produce the oil, such as Oshima Tsubaki and Kaneda. One thing to note about tsubaki oil however, is that while tsubaki oil bears the same name as the *C. japonica* variety of camellias, the oil of another variety, *Camellia sasanqua*, simply sazanka in Japanese, is also distributed as tsubaki oil. Tsubaki and sasanqua plants look very similar, and are usually distinguished by *sasanqua's* smaller flower and leaf size. *Sasanqua* petals also tend to fall off one by one, where tsubaki petals come off all at once. With regards to the growth of the plants, *sasanqua* tend to grow faster (Moor, 2020) and in cooler climates and tsubakis tend to grow to a taller height. It is believed that

*sasanquas* were originally grown for practical purposes, but by the 14th century, the decorative cultivars were prized, similar to tsubaki (Kennedy, 2016). Other than physical differences between the plants, there is not much that distinguishes tsubaki and *sasanqua* immediately.

Most secondary metabolites (SM) are derivatives of primary metabolites and are no longer essential to the plant's survival. SMs are key factors when it comes to producing perfume, agrochemicals, and cosmetics. The amount of secondary metabolites produced depends on the area of the plant (root/stems, leaves, flowers, fruits), the age of the plant, and the period of the plant's life cycle at the moment the sample is taken. The color and scent performance of a plant may be affected by secondary metabolites, such as flavonoids, terpenoids, and other volatiles can attract or repel insects and herbivores, "while toxins can be involved in plant-plant allelopathic interactions" (Hadacek, 2002).

*C. japonica* leaves have been found to produce antioxidant, anti-inflammatory (Kim et al. 2012) and anticancer medicinal compounds such as lupeol, squalene, and linalool (Majumder et al, 2020). Lupeol, most highly expressed in the leaf, is an anti-inflammatory and anti-microbial triterpene that is derived from oxidosqualene. It is perhaps the most studied of the three terpenes in conjunction with *C. japonica* because of its significance to the study of cosmetic tsubaki oil. Lupeol has been found to alleviate the toxicity induced by benzoyl peroxide, a chemical widely used in skin care products containing tsubaki oil (Saleem et al., 2001).

Linalool, on the other hand, a terpene alcohol found in flowers and plants and synthesized by linalool synthase enzymes, is perhaps more well known for being found in lavender than tsubaki. It gives off floral aromas that are often used in commercial products (Johnson, 2017). The antioxidant effects of linalool are most noticeable when absorbed by the bloodstream where it flows to the central nervous system "resulting in observed changes in mood and physiology."

Squalene, synthesized by squalene synthase enzymes, is a triterpene that is an "intermediate in the cholesterol biosynthesis pathway." Not much about squalene in relation to *C. japonica* has been studied, but the structure of squalene is nonpolar which makes it particularly compatible with oils such as tsubaki oil. A highly efficient emollient, squalene oils quickly penetrate deep skin, locking in moisture and acting as "oxygen-scavenging agent[s]" which makes it an ideal antioxidant (Huang et al., 2009). There are many papers explaining the properties of lupeol, linalool, and squalene; what is not known is if there are any differences in antioxidant properties between *sasanqua* and tsubaki species of *Camellia*. Here, we aim to identify any significant differences in expression of antioxidant synthesizing enzymes between *sasanqua* and tsubaki species of *Camellia*.

## Procedure

### Sample Collection

Leaves, seeds, and petals were collected from three *C. japonica* and four *C. sasanqua* plants from primarily the Aoyama Cemetery area.

CJ1, Itakura Food Store Hiroo, 2/9/20. CJ2, Aoyama Cemetery Nishiazabu, 2.9.20. CJ3, Aoyama Cemetery Minami Aoyama, 2/9/20. SJ1, Aoyama Cemetery Office, 2/9/20. SJ2, Aoyama Cemetery Office, 2/9/20. SJ3, Aoyama Cemetery Nishiazabu, 2/9/20. SJ4, Aoyama Cemetery Office, 2/9/20. (Figure 1 Map and legend of sample collection location)



FIGURE 1: Map and legend of *C. japonica* and *C. sasanqua* tissue sample collection locations.

TABLE 1: Primer Designs indicating forward and reverse primers for genes Squalene 1, Squalene 2, Lupeol 1, Lupeol 2, Linalool 1, Linalool 2, and housekeeping gene 18S from Li et al. (2016).

Gene	Forward Primer	Reverse Primer	Sequence ID	Amplicon size
Squalene 1	TTTCTCGCAGTTTCGCCC	AAAATGCCAGTCACGGTCA	MT151371.1 ( <i>C. vietnamensis</i> )	185
Squalene 2	GTCAAAGCTGTGGAATGCC	TTAGCAGTAAGACCACGCC	MT151371.1 ( <i>C. vietnamensis</i> )	212
Lupeol 1	CACATAGAAGGGCACAGCAT	ATCGAAAGCCAAGTCTTCCC	XM_028206589.1 ( <i>C. sinensis</i> )	176
Lupeol 2	CGGTTGGCAAGTCTCAGATT	AAGACCCTGCTTTTACTGGC	XM_028245768.1 ( <i>C. sinensis</i> )	188
Linalool 1	TAACGCCGATTCTCTTTGGG	TTCCAAACCCCATGTCACTG	XM_028239882.1 ( <i>C. sinensis</i> )	182
Linalool 2	CAGTGACATGGGGTTTGAA	CACCTTTGAACTGCCTCTGT	XM_028239882.1 ( <i>C. sinensis</i> )	198
18S (Li et al, 2016)	TCTCAACCATAAACGATGCCGACCAG	TTTCAGCCTTGCGACCATACTCCC	U42851.1 ( <i>C. japonica</i> )	119

### Primer Design

We looked for primer designs in the papers referenced but none had a design that was available and matched what we were looking for—squalene, linalool, and lupeol in *C. japonica* and *C. sasanqua*. We then used NCBI BLAST to locate nucleotides with similar sequences to *C. japonica* and *C. sasanqua* and found *Camellia sinensis* and *Camellia vietnamensis*.

Through ClustalO validated conservation, we ended up using *C. vietnamensis* for squalene as it was the most conserved. It also led us to believe we could use *C. sinensis* as a template when no other sequences were available to use for linalool and lupeol in *C. japonica* and *C. sasanqua*.

### RNA Isolation from Seedlings

*C. japonica* and *C. sasanqua* RNA were isolated using the RNA Plant and Fungi isolation kit (Takara Bio Cat. #: U0949B) and the RNA Plant Isolation Kit from Machery Nagel (Cat. #: Takara U0949S) as instructed with a few minor modifications. Samples CJ-P3, CJ-L3, CS-P2, CS-L2, CS-P1, CS-L1 were extracted using the Plant Isolation Kit, while the remaining samples were isolated using the Plant and Fungi Isolation Kit. *C. japonica* and *C. sasanqua* leaf, seed (without the shell), and petal tissue was homogenized using a mortar and pestle without liquid nitrogen. 20 mM Isopropanol was used for precipitating RNA in place of ethanol.

RNA purity and concentration was determined using a UV-Vis Spectrophotometer (Model #: ASUV-1110). Samples CS-S4 and CS-L3 were slightly yellow. A possible reason for the low 260/280 ratio, or purity, is that the samples were not fully processed until two weeks after being placed in the lysis buffer (Figure 2) and frozen at -20°C. Table 2.

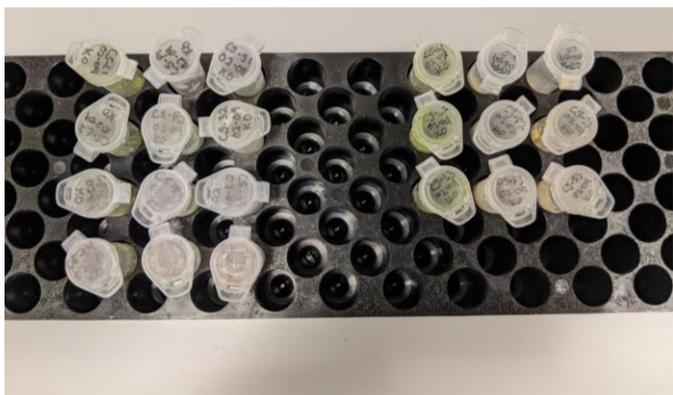


FIGURE 2: *C. japonica*, *C. sasanqua* seed, leaf, and petal tissue during RNA isolation.

#### *cDNA Synthesis*

The 1st strand of cDNA was synthesized using the PrimeScript 1st Strand cDNA Synthesis Kit as described (Cat. # 6110A). No reverse-transcriptase (no-RT) controls were also created for each biological sample.

#### *Semi-quantitative RT-PCR*

Sample CJ-L2 was used to make the amplification curve for each primer set. The sample was tested at 22, 24, 26, and 28 cycle lengths. 28 cycles were determined to be optimal for analysis. PCR were conducted as follows: 25 uL of 2X EmeraldAmp MAX PCR Master Mix (Cat. #RR320A), 1 uL of cDNA, 1uL (2 uM) each of forward and reverse primers, and 22 uL of ddH<sub>2</sub>O. All PCR conditions were as follows: 98°C for 2 minutes; 98°C for 15 seconds, 60°C for 30 seconds, and 72°C 1 minute, repeat for 28 cycles. PCR reactions were subsequently run on a 1% agarose gel using the blueGel system from MiniPCR. To quantify band size, RAW photos

were taken and analyzed using FIJI, or ImageJ Bio-Formats plug-in (Schindelin et al., 2012).

TABLE 2: Purity and Concentration of *C. japonica*, *C. sasanqua* leaf, petal, and seed tissue RNA. “CS” refers to *C. sasanqua* samples and “CJ” to *C. japonica*. “L” indicates leaf tissue, “P” indicates petal tissue, and “S” indicates seed tissue.

Sample	Ratio (260/280)	A260	Concentration (ng/μL)
CS-L1	.5	.004	16
CS-L2	1.21	.017	27.2
CJ-P1	.86	.033	52.8
CS-P2	1.375	.011	17.6
CS-S2	1.32	.037	59.2
CS-S3	.71	.103	186.8
CS-S4	1.03	0.198	316.8
CS-P1	1.14	0.016	25.6
CS-P3	0.94	0.050	80
CS-P4	1.13	0.148	236.8
CS-L3	0.96	0.105	168
CS-L4	1.11	0.113	180.8
CJ-P2	0.96	0.027	43.2
CJ-P3	1.1	0.011	17.6
CJ-L1	1.16	0.029	46.4
CJ-L2	1.22	0.084	134.4
CJ-S1	1.17	0.041	65.6

CJ-S2	1.15	0.031	49.6
CJ-S3	1.5	0.081	129.6

## Results

Our study found that, between *C. japonica* seeds and *C. sasanqua* seeds, *C. japonica* had a higher expression of linalool than *C. sasanqua* (Table 3).

TABLE 3: Gene expression of linalool, using the Lin1 primer set, in samples CJ-S2 and CS-S4. “CS” refers to *C. sasanqua* samples and “CJ” to *C. japonica*. “S” indicates seed tissue. “HKG” is housekeeping gene 18S.

Sample	True Gene Expression (% of HKG)
CJ-S2	76.1
CS-S4	51.1

Additionally, as shown in Table 4, linalool expression was also found to be higher in *C. japonica* leaves for both primers tested than in *C. japonica* seeds. Between linalool and squalene found in *C. japonica*, squalene had higher expression (Table 4).

TABLE 4: Expression of linalool and squalene in *C. japonica* leaves.

Primer	True Gene Expression (% of HKG)
Linalool 1	129.5
Linalool 2	42.2
Squalene 2	148.5

Further studies with more biological and technical replicates are advised as genomic DNA contamination may have occurred, as suggested by linalool cDNA being lower than linalool no-RT in CS-S2. It is also to be noted that primers were chosen using a degenerate primer design due to

a lack of known sequences, and consequently the Linalool 1 and 2 primers ended up with a difference in primer efficiency and therefore a difference in expression levels. Though the preliminary data suggests differences between *C. japonica* and *C. sasanqua* linalool expression, further studies are needed to determine whether these differences are significant or not.

## Conclusions

The secondary metabolites linalool, lupeol, and squalene synthases are what create linalool, lupeol, and squalene in the plants, specifically to this experiment, *C. japonica* and *C. sasanqua*. Tsubaki oil, or oil from the seeds of *C. japonica* and *C. sasanqua*, has been used cosmetically for the hair and face in Japan since ancient times, and for good reason: the three terpenes together contain antioxidant and anti-inflammatory properties which can promote the growth of hair by maintaining moisture in the scalp and follicles. Further research about the presence and concentration of secondary metabolites in various tissues of *C. japonica* and *C. sasanqua* will no doubt help our understanding of the differences between the two species, and this in turn will help tsubaki oil producers understand what to use in order to produce the best quality tsubaki oil possible.

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# Biological Warfare's Role in Colonization

Anita Osuri

Biotechnology High School, United States  
aosuri475@gmail.com

## Abstract

When reflecting on colonization, physical warfare and indoctrination are discussed, although the role of biological warfare is often undermined. The role of biological warfare in colonization efforts by the British, Spanish, German, African, and Japanese is continually debated by historians. Some historians mention the insignificance of certain biological warfare methods as being ineffective at afflicting the desired group, while other historians attest that the innate cruelty of the colonizers and the high death count impacted these power struggles greatly (Fenn, 2000). Although most biological warfare events occurred as an attack on another country, there are also instances of warfare being conducted on a country's own people. Despite the majority of attacks having happened in the 1700s - 1900s, there are many lessons that can be learnt from these brutal acts of violence. We hope to evaluate both sides of this topic through the lens of colonizers in different countries and different timeframes to uncover the true role of biological warfare in colonization efforts (Table 1).

*Keywords: COVID-19, Palliative Care, National Institutes of Health (NIH)*

## Introduction

Biological warfare, also known as bioterrorism, is an intentional release of biological agents (virus, bacteria) to cause illness or death (U.S. National Library of Medicine, 2021). From the beginning of history when the Hittites sent infected rams to their enemies to modern day with the 'anthrax letters'

being sent after the 9/11 attacks, this system of warfare has been crucial to shaping society (Greub, n.d.). As biological warfare started to become a strategic method to defeat the enemy, it also influenced colonial power struggles and possibly aided colonizers in conquering vulnerable populations. At certain points, it may have also helped indigenous peoples overcome their conquerors. Regardless of the reason, it is undeniable that although in certain continents deaths from war have decreased tremendously, there are also areas where the rate of war has increased greatly (Figure 1). The following sections will provide anecdotes, controversy, and reflections about bioterrorism's effect on colonialism specific to each continent.

### *Europe*

One of the most notable mentions of early biological warfare is the 1346 Siege of Caffa, when diseased Mongol forces catapulted troops infected with the Black Plague into the besieged city. From there, it is suspected to have transmitted to people near Crimea due to infected Italians fleeing the area (Centers for Disease Control and Prevention, n.d.). This is supported by the narrative of Gabriele De' Mussi, who describes "The dying Tartars, lost interest in the siege. But they ordered corpses to be placed in catapults and lobbed into the city in the hope that the intolerable stench would kill everyone inside." (VJ, 1966). Although there are no other sources that could corroborate this description, his account seems plausible to numerous historians after cross referencing art pieces, mortuary

records, and a modern analysis of the situation. Despite the Mongols enacting biowarfare after their inevitable loss at the Siege of Caffa, their efforts would lead to the Black Plague epidemic in Europe. The consequences would be enormous, with almost one third of Europe's population demolished, and it arguably led to the end of the Holy Roman Empire (Choi, 2013).

More recently, during World War I, during Germany's colonization attempt of Europe, they sent infected Horses with anthrax or glanders to the Allies (Roffey, Tegnell, Elgh, et al., 2014). However, since these actions did not have military consequences, they are often disregarded as minor in the war effort. During World War II, European countries would become involved in biological warfare research, although many of these efforts are argued to be minor in the war effort since they were never enacted. Some examples are rinderpest, anthrax, botulin, and Salmonella, which were tested in bombs off the coast of remote islands. However, it is suspected by some historians that these findings could have been pivotal in the war, since most data was destroyed by the end of the war or not released to the public (Roffey, Tegnell, Elgh, et al., 2014).

### *Asia*

Asian colonization was categorized by European and Japanese imperialism, specifically within the Middle East, the Indian Subcontinent, and Southeast Asia (Encyclopædia Britannica inc, n.d.). Since the beginning of European colonization in East Asia, there have been unintentional transfers of disease. Most notably, in China malaria would eventually affect more than 30 million people annually by the mid 1940s (Park, 2011). Due to the devastating effect of malaria on weakening their people and the country, Hong Kong created numerous antimalarial efforts and became one of the first leaders in public health and disease prevention.

As Japanese imperialism advanced in World War II, there were increasingly unethical experiments being performed on the colonized

individuals. For instance, many people from China were kidnapped and infected with disease, then dissected to view how said disease affected the body. These research experiments were used to help the Japanese develop plague bombs and aided in their plans to colonize Asia (Nicholas, 1995). These plague bombs were later dropped on Chinese cities to see how effective they were at creating pandemics. The unique Japanese example demonstrates how biological warfare not only aids colonizers with suppressing vulnerable groups, but also leads to increased knowledge in science and inevitably progresses understanding about the world.

During the Korean War, the United States was also controversially suspected of dropping bombs containing fleas over devastated Korean battlefields to spread plagues ravaging the area such as typhus (JAMA, 2011). However, these accounts are opposed by historians who attest that these diseases were endemic to the area and that these stories were rumors meant to spread propaganda against the United States.

### *Africa*

Africa has faced colonization by various countries over the years including Britain, France, Spain, and more. However, to most historians the most shocking instances of biowarfare in the continent are those done to their own citizens. Although not officially motivated by colonialism of another country, it can be argued that the South African apartheid biowarfare program was an attempt to colonize and suppress their own people. The program named Project Coast included "human experiments, plots of mass murder using poisoned beer and anthrax, assassinations attempts through poisoned clothes, tampered tools and exploding letters" (Chutel, n.d.). The victims of these projects were South African residents who spoke out against Apartheid including Desmond Tutu, who received a threat of an experimented baboon fetus due to his human rights activism.

## *The Americas (North America and South America)*

One of the most famous instances of colonialism is the Spanish and British conquest of the Americas. There has been a contended debate on whether Gen. Jeffrey Amherst infected local Native Americans with items from a smallpox hospital (Fenn, 2000). Although the idea is implied in one of Gen. Amherst's letters, it is still uncertain, and the smallpox infected Native Americans could have arisen from many other avenues. However, the idea of infecting Native Americans with infectious disease in the start to taking over the area was not a new notion. In fact, one account states, "we gave them two Blankets and an Handkerchief out of the Small Pox Hospital. I hope it will have the desired effect" (Frischknecht, 2003). This cryptic message suggests that the infection was deliberate and part of a methodical plan to harm the native population.

More recently during the 1950s, biological warfare was tested on United States' residents to prevent a possible colonization attempt overseas. The military sprayed a fog with potentially harmful microbes into San Francisco to see how a biological weapon would affect the 800,000-resident city (Loria, 2016). One patient died from *S. marcescens* as an infection spread to his heart. Although this instance was meant with positive intentions to deter possible biowarfare attacks through knowledge, it provokes scientists and historians alike to consider the ethics of such testing on a country's own citizens.

## **Conclusion**

Biowarfare has been around since the beginning of humanity, and has continued to become an important topic of discussion in modern society. The impact of biowarfare cannot be understated as it has shaped society, especially with colonization, whether offensively or in attempts to deter attacks. These instances emphasize the importance of more discussions on the ethics of such actions and the regulations or transparency

governments should maintain with their residents. Especially with government internet security and the controversial handling of Covid-19 by numerous countries at the forefront of the conversation, these are crucial questions to ask for the safety of future generations.

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# Mexico's National Electoral Institute: Lessons from Current Progress, Shortcomings, and Citizen Response

Juan Sandoval

American School Foundation of Monterrey, Mexico  
22sandoval8631@asfm.mx

## Abstract

The National Electoral Institute (INE) has been a driving force for democratization in Mexico and a prevalent actor in both federal and regional elections. Previously known as the Federal Electoral Institute (IFE) and reformed in 2014, this independent electoral commission has gone beyond ensuring safe elections on ballot day; the INE expanded access to voting, made significant strides for gender equity in government, regulated campaigning, and attempted to ensure fair elections in Mexico. As the INE grows and develops its functions and role in the country, both successes and difficulties have arisen. This systematic literature review employed the academic database, Google Scholar, and other relevant articles to understand the regulatory agency's accomplishments and failures and what both the INE and other electoral commissions can learn from them. Media regulation, working conditions, and regional mismanagement are among some of the topics explored. Public perception of the organization is also examined, investigating the root causes for the trust, or lack thereof, in the INE and what can be done to best legitimize the agency in order to serve its constituents best.

*Keywords: INE, elections, Mexico, electoral reform.*

## Introduction

Since the early 2000s, Mexico has transitioned from a one-party state to an internationally recognized democracy. Many credit the National Electoral Institute (INE), previously known as the Federal Electoral Institute (IFE), for this change (Acosta, 2008). The National Electoral Institute's primary function is to aid in "organizing federal elections [and organize], in coordination with the electoral bodies of the federative entities, local elections in the states of the Republic and Mexico City" (Instituto Nacional Electoral, 2021). The entity's roles have expanded in recent years, with significant strides and ongoing challenges. However, it is important to first understand the history that called for such an organization in the first place.

In the twentieth century, the Institutional Revolutionary Party (PRI) was the sole winner in national elections and had complete control over the nation; the country was a one-party state (Acosta, 2008). Though PRI had a stable government and fair approval, this hold on power was heavily authoritarian. In order to transition to a democratic state, many insisted that other parties must be represented fairly in national elections and have an opportunity to win the presidency.

Some challenges PRI faced certainly helped accelerate this process of change in government toward the end of the century. For example, their poor handling of the 1985 earthquake drew heavy

criticism from many citizens, shedding light on mismanagement of funds, resources, and poor organization (Tavera-Fenollosa, 1998). Just a year before that, when hosting the 1984 Olympics, the PRI had used brute coercion to silence citizens in their protest for better education. Ultimately, the 1994 Zapatista movement in the southern states, which protested indigenous rights and socioeconomic inequalities between the north and south states, was the breaking point for the PRI (Schulz, 2007). This movement brought along fighting, instability, and violence, leaving many to hope for a safer state and a government that brought order, peace, and equality to all citizens.

The people who held office also played a role in decreasing party trust. In 1994, the leading PRI candidate— Luis Donaldo Colosio Murrieta— was assassinated, ultimately replaced by an inexperienced candidate who was not favored by the public. Although the new PRI candidate, Ernesto Zedillo (1994-2000), won the elections that year, his rule was criticized, and the party lost some of its legitimacy and trust (Rodríguez, 2003). This set the stage for one of the first truly competitive elections in 2000, as the PRI did not comfortably lead in the polls. At this time, the IFE (now INE) was of critical importance in ensuring the outcome would be fair and democratic (Woldenberg, 2001).

In 1990, the IFE was established by a series of constitutional reforms and the Federal Code of Electoral Institutions and Procedures. Political parties, the national government, and even citizens participated in its creation (Instituto Nacional Electoral, 2021). In 1996, several reforms were introduced to this body that detached the entity from the federal government, allowing for greater autonomy and accountability (McNally, 2014). The IFE oversaw the 2000 presidential elections, where, for the first time, a party other than the PRI was victorious. Vicente Fox (2000-2006) from The National Action Party (PAN) took office, symbolizing democratization in Mexico and legitimate elections. Many credit IFE

for ensuring fair elections, and the body continued to participate both locally and federally (Acosta, 2008).

In 2014, the Enrique Peña Nieto administration (2012-2018) instituted reforms to the body again, changing its name to the National Electoral Institute (INE). Among these was greater regional participation of the INE in elections, as some of these were still regarded as heavily corrupt and illegitimate, despite significant advances in national elections (Estévez et al., 2008). Other changes included increased power of the INE to regulate campaign financing and media use, institute gender equity initiatives, and promote greater voter turnout. These changes have expanded the body's functions significantly, which has come with several benefits and drawbacks. This paper seeks to determine what other autonomous election regulatory bodies can learn from INE's current role in the nation and what Mexican citizens think of the INE itself.

## Methods

A comprehensive analysis of both quantitative and qualitative data was carried out through a systematic review of literature; this method allowed for the consideration of multiple perspectives and an effective synthesis (Cooper, 2010). The qualitative study follows specific and replicable steps; keywords were used to narrow the search, and all of the documents taken into account were in English or Spanish (the author's native language).

Entering the search terms (such as "IFE" AND "elections," "INE," OR "National Electoral Institute") in the Google Scholar academic database yielded (n = 2034) results, and (n = 96) relevant papers were screened. Various iterations of "INE" such as "Mexican elections body" and "election regulation in Mexico" were included to broaden sensitivity while maintaining specificity. Each of them was evaluated thoroughly on whether they should be included in the final set (relevancy, quality, and credibility were assessed). A PRISMA 2009 checklist was used to

guide this process and keep track of source information (Moher et al., 2009). From the papers screened, (n = 54) papers were excluded due to irrelevance to the review. This included the discussion of IFE policies that are now not enforced and lack relevance to the current INE rules and roles. Others focused on the transition of Mexico to a democracy in 2000, without expanding much on the agency's role after that election. (n = 42) full-text articles were assessed for eligibility. These papers were reviewed and tracked in a spreadsheet. The use of papers in the Spanish language allowed for a more robust set of sources and academic works.

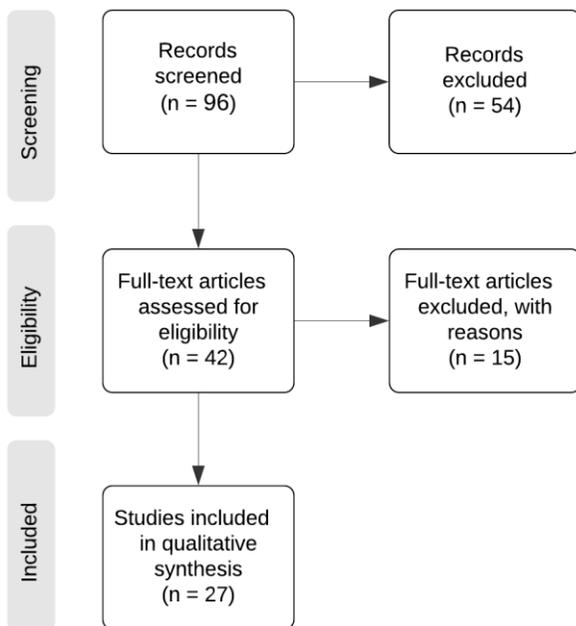


FIGURE 1: Vetting process for systematic literature review

Some news articles about current events relating to the INE's recent decisions were also included in the review, but these were not opinion news sites; rather, these sources merely provided information on actions the body has recently taken and provided statements from relevant parties involved in each situation. These sites were all screened using JBI's critical appraisal tools for legitimacy, credibility, lack of bias, and

reliability (Joanna Briggs Institute, 2021). INE's own website was also used as a primary source. All information sources used were from peer-reviewed journals, works from accredited academic institutions, trusted news sites, and sites from national agencies and trusted organizations; therefore, the data used in this synthesis is reliable and credible.

### Areas of Success since 2014

There is no doubt that the National Electoral Institute (INE) was a prominent actor in Mexico's transition to democracy. It has been a trusted body that has allowed the nation to conduct legitimate federal elections that are, for the most part, free and fair (Ruíz, 2014). Apart from this, INE has provided multiple benefits to elections that are worth mentioning and examining.

One of the main changes in the 2014 reform and change from INE to IFE was the wider presence of the regulatory agency in regional elections. Often, these were subject to severe corruption by parties like PRI, who held on to power locally by using methods such as ballot stuffing and paying constituents for party loyalty in local elections (Cruz, 2014). In addition, municipalities and states had their own electoral commissions, which were not as reliable and robust as the IFE. The control of the INE in these elections after 2014 has allowed for more fair elections on the regional scale, one of the primary purposes in the creation of the INE (Torres Rodríguez, 2019).

The electoral institute, however, goes beyond election regulation and anti-corruption efforts. For example, gender quotas have been instituted by INE, setting rules on party candidates with a 50% quota for women candidates in congressional and regional elections. Many have acclaimed this step, seen as a good first step in gender equality in politics (Figueroa, 2017).

The INE has also directed its efforts to promote equal access to voting for all citizens at both the state and national levels. Increasing

voter participation and turnout has always been one of their major goals, and they have made significant progress in those efforts (Pedroza, 2015). As a result, Mexico's turnout in both regional and national elections performs above many other nations in Latin America (Sonneland, 2018).

Lastly, the INE has conducted election polls that objectively analyze candidate performance well before the election (Mendoza & Nieto-Barajas, 2016). This ensures that an added level of security as it effectively sets a data trend where discrepancies in the actual election are easily noted. If the results on election night vary with poll results, then recounts and other measures may be instituted, fortifying legitimacy. However, this data is not released to the general public, eliminating transparency and casting doubt on practice; this is one of the many practices the INE conducts that the public criticizes (Nájera, 2015). Below, other challenges the body has recently faced are explored in detail.

some arguing that the regulatory agency, although following their protocol, may be acquiring too much control (González et al., 2021). A notable example was intending to punish Mariana Rodriguez, wife of newly-elected governor Samuel Garcia of Nuevo Leon, for using her social media platforms (Instagram, Facebook, Twitter) to spread the word about her husband's campaign (Expansión Política, 2021). Critics say this action may infringe on the right to freedom of expression and speech, for which the INE has been criticized extensively (González et al., 2021).

One other concern citizens had about the INE is how they hire their workers, who they often call "volunteers." For that same reason, many of their workers are paid less than minimum wage, resulting in heavy criticism from the public (Cantala & Sempere, 2015). The organization's selection process for workers has also been cast into doubt, as there have been reports of ballot stuffing conducted by INE personnel in several regional elections (Cantú, 2019).

The current President, Andres Manuel Lopez Obrador, has also disapproved of the autonomous body (Oxford Analytica, 2021). He says that they have failed to ensure safe and fair voting practices and are corrupt in nature. In addition, he has criticized the INE's failure to conduct and encourage turnout in the National Popular Poll (which AMLO said would strongly favor him). This has presented a significant challenge to the INE, as their image has been tarnished since Mr. Obrador's comments may influence the president's supporters (Peschard, 2021).

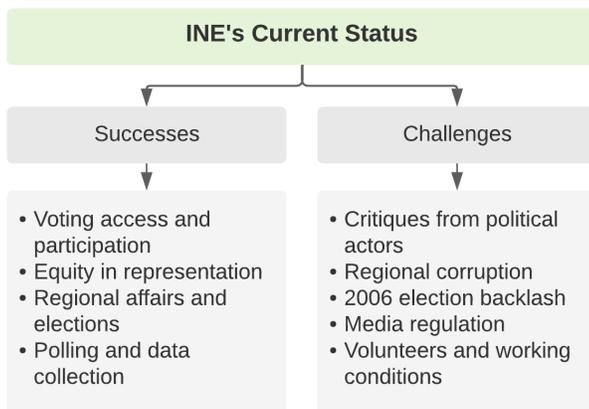


FIGURE 2: Summary of INE's successes and challenges.

### Current Obstacles and Criticism

Mexican political parties must follow a myriad of rules for TV appearances and the use of social media in campaigns (Instituto Nacional Electoral, 2021). These stringent rules have put various individuals and parties in trouble, with

### Public Perception

Although Mexican citizens have historically trusted the INE due to its role in instituting democracy in the nation, its legitimacy and trustworthiness have fallen in recent years (Pérez-Verduzco, 2020). A 2019 poll conducted by the Mitofsky Association found that trust in the INE fell behind other notable institutions and platforms

like the military, the president, and even social media (Consulta Mitofsky, 2019). Many credit some of the aforementioned shortcomings and general distrust in Mexican public and governmental institutions. It is important to mention that trust in elections themselves has not fallen as quickly, making it clear that other factors within INE itself play a role in public perception (Gómez, 2011).

One of the most influential events in the deterioration of the INE's public trust was the 2006 presidential election (Jackson, 2014). This was a significant challenge for the regulatory body as the results were heavily disputed and challenged. One of the candidates, Andres Manuel Lopez Obrador (now president, 2018-2024), called for a recount and blamed the IFE (now INE) for failing to ensure a fair and democratic process. According to general consensus, the IFE had been unable to safeguard a legitimate election (Ortega & Somuano, 2014). The 2006 election continues to impact the entity's legitimacy to this date, as questions about its true autonomy and effectiveness still linger on the public's mind, leaving a salty taste of what was a poorly organized process and questionable outcome (Jackson, 2014).

### **Conclusion and Discussion**

The INE has undoubtedly had a significant impact on Mexico, leading the way for democratization and legitimate elections in the country. However, this institution has expanded beyond the role of making elections safer and fairer at voting day; it has taken significant steps to venture out into other areas of public service and political action (McNally, 2014). Voting rights, access, and equity continue to be an ongoing point of focus for the INE as they expand their reach geographically and virtually (with social media). However, the lack of trust in the organization has hindered some of this progress, as citizens do not see this body as truly independent and reliable (Valverde, 2019). The INE must work to ensure that regional elections are entirely rightful since perpetual

scandals in these elections delegitimize the organization.

The INE must also publicly address the 2006 election and ensure voters that the same mistakes and mismanagement will not occur again. Working together with the legislative branch to propose measures like partnerships with regional agencies and initiatives like the implementation of more modern voting machines could aim in this effort, showing the public that guidelines would prevent further attempts (mostly regionally) to commit fraud. Releasing their poll data before elections is also essential in establishing trust in the body, ensuring complete transparency throughout the voting process.

It is without a doubt that INE has also taken other roles that have made progress beyond election day. For example, women's quotas for nomination have proven to be an effective method of gender equality in the Mexican political process (Figueroa, 2017). Other nations like Argentina and Chile have instituted similar programs that have been beneficial at increasing representation, showing the widespread success of such actions (Gray, 2003). The INE ought to continue to focus on expanding its role with initiatives like this, basing them on the needs of citizens. The use of polls and existing national data could be helpful in determining what these priorities are for the Mexican public.

One of the limitations of this paper is that the data relating to the body is fairly recent and limited, making it difficult to thoroughly analyze the successes and failures of the newly-instituted body in complete certainty. However, situations relating to the IFE that still apply to the new organization serve to fill those knowledge gaps. Additionally, this paper primarily focused on the organization's efforts pertaining to traditional voting; although the topics of gender equity and media were touched upon, they could be explored in much further detail as they have been central in Mexico's political and social identity and continue to offer important pieces of information and for analysis.

Therefore, further research could expand on some of the various avenues the INE has taken in recent years, particularly gender equity in the electoral process. Furthermore, investigating the effectiveness of quotas not only in women's representation but also in the policy that is passed as a result of a more diverse body is of critical importance to understanding the extent to which the INE has played in this front. Lastly, more public opinion polls regarding the reasons for discontent with the organization must be conducted to better understand the reasons for falling confidence in the INE; this way, the organization can implement appropriate changes to legitimize itself further and be able to effectively regulate elections with complete trust from the public.

In hindsight, the INE must ensure that it functions in complete service to the public and democracy; they must be able to safely regulate voting at both the national and regional level and regain trust from the public to continue to function in a manner that made them the leading force to democratization in twenty-first-century Mexico.

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# A Systematic Review of Communication and Health Literacy Barriers in Healthcare

Reeya Sannake

Rochester Adams High School, United States

reeyasannake1@gmail.com

## Abstract

With modern technology, healthcare is advancing, but there are still barriers present in healthcare. As the population grows, the barriers become more glaring and evident. Through research of literature, data, statistics, and recorded audios on communication and health literacy barriers to healthcare. Communication and health literacy has often been misguided by the public. In my research paper, the following has been noted about the barriers; (i) patients have a hard time raising the voice due to fear and embarrassment; (ii) patients often leave out crucial information; (iii) healthcare professionals don't create flow between conversation by focusing mostly on the notes and not the patient; (iv) factors that impact health literacy include race, gender, and poverty; (v) health literacy can impact a person's life and can misguide their diagnosis; (vi) having pamphlets and instructions that are easy to read have proven to increase health literacy. In order to address these barriers, there are several proposals in my research paper for both communication and health literacy methods. For example, respecting cultural differences and language barriers, having easy to read pamphlets and reading doctor approved online on specific health conditions, and offering longer conversation. Overall, these proposals could reduce the effect on the barriers in healthcare.

*Keywords: Healthcare, Communication, Health literacy*

## Introduction

Healthcare has been advancing for the past century, but there are still barriers present in healthcare such as medication, insurance, communication, transportation, and health literacy. The aim of this systematic review was to address the barriers in healthcare discussing communication and health literacy. Communication between patient and doctor is important, and miscommunication in the health sector can be life-threatening (Meuter et al., 2015). The increasing percentage of patients makes the issue of inadequate access to communication pressing. Communication barriers exist between both the patient and the healthcare professional. Patients' related factors include misleading information, being scared to speak up due to embarrassment, etc. As much as there are patient related factors, there are healthcare professionals related factors. Healthcare professionals related factors include talking down, not taking good notes, and not instigating enough flow in conversations. As both patients and healthcare professionals have trouble with communication, sometimes the result can be dangerous and often can take someone's life. "Although many terminally ill people are admitted to an intensive care unit (ICU) at the end of life, their care is often inadequate because of poor communication by physicians and lack of patient- and family-centred care (Visser et

al.,2014). As important as communication is, so is health literacy. "Literacy is defined as the basic ability to read and speak English, whereas functional health literacy is the ability to read, understand, and act on health information. Up to 48% of English-speaking patients do not have adequate functional health literacy"(Andrus et al., 2012). The consequences of poor health literacy are more frequent visits to the ICU, poor health status, and lack of knowledge on specific health diagnosis. Health literacy is crucial to empowerment. "Health literacy is clearly dependent upon levels of fundamental literacy and associated cognitive development. Individuals with undeveloped skills in reading and writing will not only have less exposure to traditional health education, but also less developed skills to act upon the information received" (Nutbeam, 2000). These individuals would have less knowledge on their conditions and specific health chronic diseases, and are more likely to produce medication errors (Kountz, 2015). Healthcare has many barriers, but the ones that are overlooked are communication and health literacy.

## Methods

Researched using research papers, compiled data, databases, recorded videos, and statistics. Papers were taken from search engines such as Google Scholar and Pubmed. Figures were taken from publicly accessible data. The search keywords used were communication, healthcare, and health literacy with the category of barriers and healthcare to broaden the search. Figures were created using google sheets and Google Slides.

## Discussion

### *Communication Barriers to Healthcare*

Communication has been a barrier in different aspects, especially in healthcare. Communication is not one-sided, and it requires both the patient and the healthcare professional to step in. Many of the communication barriers come from both the

patient and the doctor. From the patient's side; (i) patients have a hard time raising their voice due to embarrassment or being scared, and that can lead to the patient not talking and not setting the relationship they want with the doctor; (ii) withholding information is serious and can alter the treatment or diagnosis if not given important information such as family history, social history, allergies, etc.; (iii) not asking follow-up questions or preparing before the visit will cause the patient to forget the information retrieved about medications, diagnosis, etc. (Emery, 2020). As much as there is a patient's barrier in communication, there is the communication barrier in doctors. From the doctor's side; (i) using medical terms that are not known to the patient which can lead to confusion; (ii) talking to patients with urge that they are too busy can make the patient hesitant to ask questions; (iii) focusing on writing notes instead of the patient leads to inconsistent flow of conversation (Emery, 2020). Medical schools have been criticized for not developing communication training, respecting, and ensuring trust in patients (Butler et al., 2021). We can't forget about the cultural and language differences between patients and doctors. "Cultural differences can cause misunderstandings between patients and doctors. Realizing how culture can influence a person's perceptions of health and medicine can really make a difference in understanding a person's medical needs and how to communicate with them" (Powell, 2021). Also, Covid-19 has impacted communication between doctors and patients even more than before. As much as face masks are important, it added a layer of barrier between patient and doctor communication. "The use of face masks also has a detrimental effect on information exchange, shared decision-making, and patient adherence to medical advice" (Ogunbiyi, 2017). This is an unsettling barrier to all patients, but especially patients with disability. Communication is a barrier that is often overlooked and needs to be addressed.

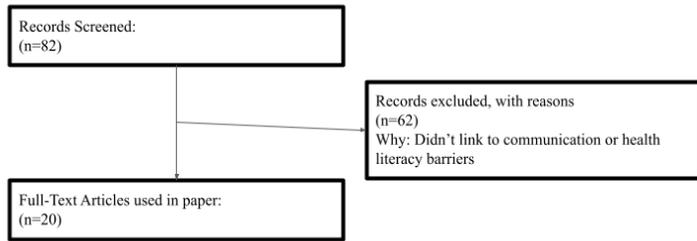


FIGURE 1. Prisma flow diagram of research paper

### Health Literacy barriers to Healthcare

“The U.S. Department of Health and Human Services (HHS) defines health literacy as “the degree to which individuals have the capacity to obtain, process, and understand basic health information needed to make appropriate health decisions” (HealthyPeople.gov, 2020). Factors that impact health literacy include a patient’s capacity to process, obtain, and receive information. If patients are given health communication materials, they have to be able to process and obtain the information, or else the patient education isn’t effective. Factors that can influence health literacy can range from education, race/ethnicity, age, and disability. High literacy rates are the least in Hispanic, Asian, Pacific Islander, Native Hawaiian and more in Multiracial/other races, whites, and blacks [Figure 2].

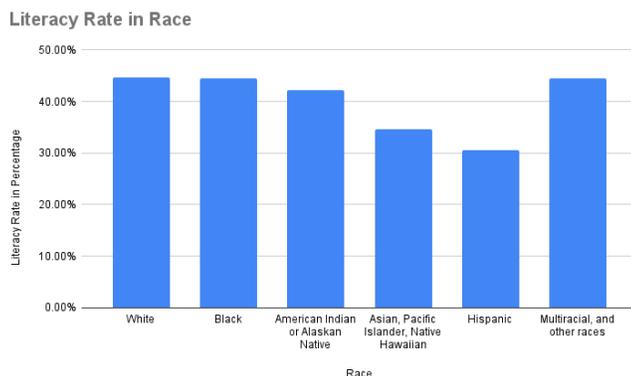


FIGURE 2. High Literacy rate data within different races in 2016. Data retrieved from CDC analysis of BRFSS health literacy data in 2016.

Poverty can impact health literacy to be lower. People with low English proficiency have lower rates of health literacy than English proficient. Individuals with low health literacy have experienced greater health care use and medical costs than those with proficient health literacy (Mahadevan, 2013). Studies also have found that adults with Medicare insurance have low health literacy, plus more visits to the ER and hospital admissions” (HealthyPeople.gov, 2020). A study was conducted within the Primary care within the Sioux Falls Area, where there are both English and Spanish health education brochures. Several physicians said they had a method in place for people with low health literacy patients, but none were using a formal test. The results came, and only six physicians could name a community resource that assists low health literacy patients (Seurer et al., 2013). Caring for patients is difficult, especially with language and low health literacy barriers. It is why learning from step one on how to care for low health literacy patients and how to reduce the number of low health literacy patients is crucially important. In the United States state counties' health literacy scores average around basic and intermediate which are identified as scores 184-225 (basic) and 226-309 (intermediate) [Figure 3].

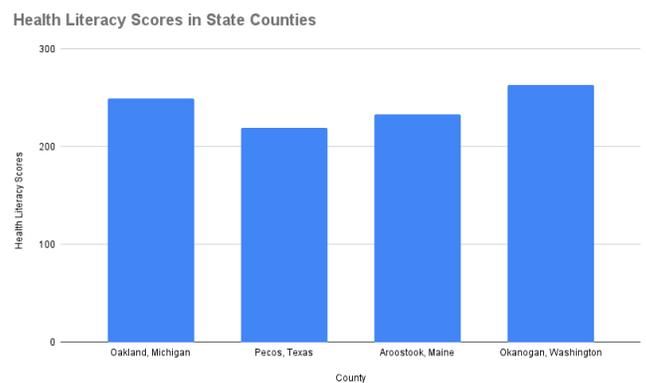


FIGURE 3. Health literacy scores in Michigan, Texas, Maine, Washington counties in 2014. Health literacy scores below 184 are identified as

below basic, scores 184-225 are known as basic, health literacy scores 226 -309 are known as intermediate, and proficient health literacy scores are considered 310-500. Data retrieved from University of North Carolina at Chapel Hill.

Adults with basic health literacy rates are classified as identifying medical information but have difficulty applying to their specific health context (University of North Carolina at Chapel Hill, 2015). Intermediate are known to understand and apply the information to their specific health context. (University of North Carolina at Chapel Hill, 2015). “Medical education has a role to play as well in ensuring that adequate numbers of future physicians are able to meet the linguistic needs of this country’s diverse population” (Tauqeer, 2017). Covid-19 has impacted people with low health literacy. “For instance, in Europe, nearly half of adults reported having problems with health literacy and not having relevant competencies to take care of their health and that of others” (Paakkari et al., 2020). The development of situations like Covid-9 is very important and needs urgent care and requirements. Measures have been taken such as 6 feet (1.83 m) distance, mask mandatory, and outdoor gathering restrictions. “Importantly, nations should invest in the health literacy of citizens that could help people to reduce the risk of infection spreading and understand the reasons behind the social responsibility and disease prevention” (Latif, 2020). Health Literacy, the ability to find, understand, and apply health information, has become an important part now more than ever for people to navigate during tough times (Covid-HL Network, 2021).

## Proposals

### *Communication proposals*

Communication between healthcare professionals and the patient has not been overall pleasant or satisfying due to not developing a relationship between healthcare professional and the patient and having a lack of communication

skills (Norouzinia et al., 2015). Here I propose that: (i) having longer discussions, frequent visits, simpler language for medical terms, using visuals, and willing to be their friend will bring the relationship closer and healthier to both the patient and the healthcare professional; (ii) respecting and understanding more of the patient’s background before the visit can better enhance understanding of the patient and make the patient more comfortable talking to the healthcare professional; (iii) adjusting to their needs and knowing boundaries can make the patient more comfortable telling you about their visit; (iv) Medical schools should incorporate more virtual tech sessions to teach communication barriers during pandemics like Covid-19, incorporating can ensure that future doctors are prepared for the next pandemic and establishing would shape the future generation (Ogunbiyi, 2017). Communication barriers impede patients and healthcare professionals all over the world searching for better relationships; my proposals could reduce these barriers.

### *Health Literacy proposals*

Health literacy barriers in healthcare include inadequate information from doctor to patient, using the internet for diagnosis, and having challenges understanding. “Lower health literacy has been associated with a higher prevalence of depressive symptoms, physical limitations, and chronic diseases; specifically heart disease, diabetes, stroke, and asthma (Vecchiarelli, 2018).” Research shows that health literate patients are able to make better lifestyle choices, be able to access information, and have better communication with healthcare providers, etc (Vancouver Coastal Health, 2014). In order to increase health literate within patients I propose that; (i) Making information, patient diagnosis, pamphlets, and medications instruction easier to read (e.g., at a fifth-grade reading level) can increase health literacy in patients; (ii) Having websites created by healthcare professional that are credited for being accurate for patients to

easier read electronically at home for better understanding; (iii) include a Q&A for patients after visits for any additional information about their diagnosis to further enhance their understanding. Advocating these proposals can provide patients with higher literacy rates than before.

## Conclusion

It is evident that healthcare has barriers, especially in communication and health literacy. Communication and health literacy barriers proposals should be addressed. Despite the limitations of my web-based searches and investigations, including our inability to collect data and interview healthcare professionals and patients. Common communication barriers include withholding information, using medical terms not known to patients by doctors, and not incorporating in medical school how to handle patients with language and cultural barriers. Patients with low English proficiency and cultural differences are the most at risk with communication barriers. Communication proposals include having longer discussions, incorporating more lessons in medical school, respecting and learning more about the patient's background before the visit, etc. Advancing communication between doctor and patient can improve health literacy rates in patients by more moral and informative discussions. Having easy to read pamphlets, more detailed notes, including a Q&A for patients, and having electronically accessible patient information could increase health literacy rate in patients and the public. By diminishing barriers in healthcare, people would know how to take care of their health and ensure they have a good relationship with their doctor.

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# Human Visualization of Brain Tumor Classifications using Deep CNN: Xception + BiGRU

Ashley Minsuh Seong

Seoul International School, Republic of Korea

seong.ashley.0308@gmail.com

## Abstract

Throughout the world, brain tumors have become a medical priority as more people suffer from this malignant disease worldwide. In the field of computer science, researchers have been studying to utilize MRI scans to its fullest potential, in recognizing signs of tumors early on, and utilizing computers and convolutional neural networks to process massive amounts of patient data at once in hopes of saving lives. This investigation finds out the specifications of visualization of MRI scans and how filters and layers are used to identify lethal tumors in the brain. For one of our main methods, a pre-trained model to improve accuracy was used - the Xception model. This showed a contrast between previous existing models as those fully connected layers were added to the back of existing ones. Our main proposed model of Xception + Bidirectional GRU had the highest accuracy of 82% out of 7 different models. In our proposed model, Convolutional layers were used to extract specific features of an image and process other similar images in the same way. By using 3 layers of Convolution, Activation, and Max pooling, we saw the networks focus on the actual tumors in the brain by distinguishing patterns in images and focusing on that area to create visual representations. Principal components of this research were the ability to visualize abnormal features of brain scan images to filter out and layer regions to bring attention to tumors in the brain.

*Keywords: Brain Tumor, Deep CNN, Xception, BiGRU*

## Introduction

### *Background*

Cancer has become a medical phenomenon that contributes to the highest death rates around the world. Incidence rates remain consistently high in high-income countries (HIC), but the prevalence of risk factors including obesity, smoking, and physical inactivity has led to low and middle-income countries (LMIC) to have high rates of cancer as well [1]. As a result of this increase, cancer has become a known threat. However, brain cancer has been and is considered one of the most lethal and malignant cancers in people of all ages because the nervous system works directly with the brain to control the entirety of bodily function [2]. Out of the various types of brain cancer, pituitary tumor, meningioma tumor, and glioma tumors are focused throughout this article.

Approximately 238,000 new cases of brain and central nervous system cancer are diagnosed annually [3]. Although brain and nervous system cancers account for 3% of all cancers in the world, they have a mortality rate of 3.4 per 100,000 people [4]. Despite having a low overall mortality rate, these tumors are also one of the most common tumors in adolescence (21%) and have become the first leading cause of cancer deaths for males aged under 40 years and females aged under 20 years [5].

As brain cancer becomes a prevalent issue around the globe, methods of receiving faster and more accurate identification have come into question. Magnetic Resonance Imaging (MRI) scans have been long used to look at structures inside human bodies. However, new fields in medical science have built neural networks to train artificial intelligence [6]. Researchers at NYU Grossman School of Medicine in collaboration with Facebook AI were able to significantly analyze to what extent AI can accelerate MRI scanning and processing. They were able to remove roughly three-fourths of raw data and generate fast MRI scans that matched the standard, slower MRI process. As the AI MRI scans required up to four times less data than the standard, patient imaging was much faster and as a result spent less time in the actual MRI machines. Through this study, researchers were able to underscore the clear benefits of investing in artificial intelligence in the medical field regarding MRI scans.

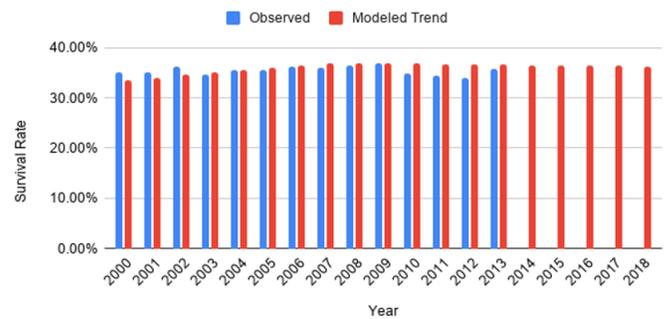
Although mortality rates of cancer originating from the brain are relatively low, mortality rates caused by metastasis (spread of cancer to other body parts) to the brain is high. This is an area of concern as the brain is one of the body's organs where metastasis occurs at a frequent rate. As metastasis has limited effective treatment and is difficult to identify and diagnose, patients' median survival rates are only a few months [7].

FIGURE 1. 5-year relatives survival rate for brain and other nervous system cancers from 2000 to 2018

Figure 1. Using a data set from (<https://seer.cancer.gov/statfacts/html/brain.html>), a graph was created comparing the 5-year survival rate (SEER 9) for brain and other nervous system cancers, with observed statistics versus the modeled trend. For years 2014-2018, observed data was not available, but the predicted model trends were given.

### Objective

5 Year Relative Survival Rate (SEER 9) for Brain and Other Nervous System Cancers



Our main objectives are to (i) adopt and incorporate deep learning techniques with pre trained Convolutional Neural Network models with fine tuning to fully quantify and classify brain tumor images, (ii) deliver them in a functioning high level of accuracy, (iii) bolster and underscore the efficiency of our method compared to traditional transfer learning and propagation neural network techniques, (iv) justify the use of 4 classifications: meningioma, glioma, pituitary tumors, and normal MRI scans compared to the typical 3 classifications, and (v) explore the usage of heatmaps in MRI scan images to portray anomaly sections of the brain. This paper will now explore contrasting related works, our material and methods used, results, discussions, and conclusions.

### Related Works

Swato et al., have used a public CE-MRI data set (Cheng, 2017) to train convolutional neural networks for specific types of brain cancers. This article used a pre-trained deep CNN model and a block-wise fine-tuning strategy to evaluate CE-MRI datasets. They were able to achieve an average accuracy of 94.82% under five-fold cross-validation and used traditional machine learning incorporated with deep learning methods using CNNs. They classified three types of brain tumors: meningioma, glioma, and pituitary tumors [8].

Deepak et al., used a pre-trained GoogLeNet to identify and analyze MRI images of the brain. This

experiment used a similar five-fold cross-validation process from an MRI dataset on figshare, outputting an accuracy of 98%. This paper specifically evaluated the system with fewer training samples and implied transfer learning as a useful technique in limited medical imaging. They classified three types of brain tumors: meningioma, glioma, and pituitary tumors [9].

Sumitra et al., suggested Neural Network techniques for classification of MRI of the human brain. The PCA and Neural Network technique utilized dimensionality reduction, feature extraction, and classification. The Back Propagation Neural Network classifier classified subjects as normal, benign, and malignant images. The accuracy for this method was ranging from 100% to 73%. BPN was used to train, test, and classify tumors for its fast-training speed [10].

Seetha et al., used Fuzzy C Means based segmentation, texture, and shape feature extractions. They further used SVM and DNN based classifications to result in tumor or normal brain images. CNN used a deep learning method, using image net database pre-trained models. This method showed the training accuracy to be 97.5% [11].

Afshar et al., found CNNs to require large amounts of data, therefore switching to capsule networking that proposed to revolutionize deep learning. Capsule networks were found to be robust to rotation and affine transformation and required less training data, specifically targeting CNN's flaws. The accuracy found for CapsNet imaging was 78%, while CNN's accuracy imaging was at 61.97%. Therefore, the Capsule networks efficiently overcame the shortcomings of CNN [12].

## Materials and Method

### *Data Description*

Data set used involved two sections: testing and training. With 4 classifications, there were glioma tumor, meningioma tumor, pituitary tumor, and no tumor. The testing files contained 100 files for glioma tumor, 115 files for meningioma tumor, 74 files for pituitary tumors, and 105 files for no tumors. For the training set, glioma tumor carried 826 files, meningioma tumor carried 822 files, pituitary tumor had 827 files, and no tumor carried 395 files. Overall, 3264 files were used in our data set. This data set can be analyzed and credited in this link:

<https://www.kaggle.com/sartajbhuvaji/brain-tumor-classification-mri?select=Training> [13].

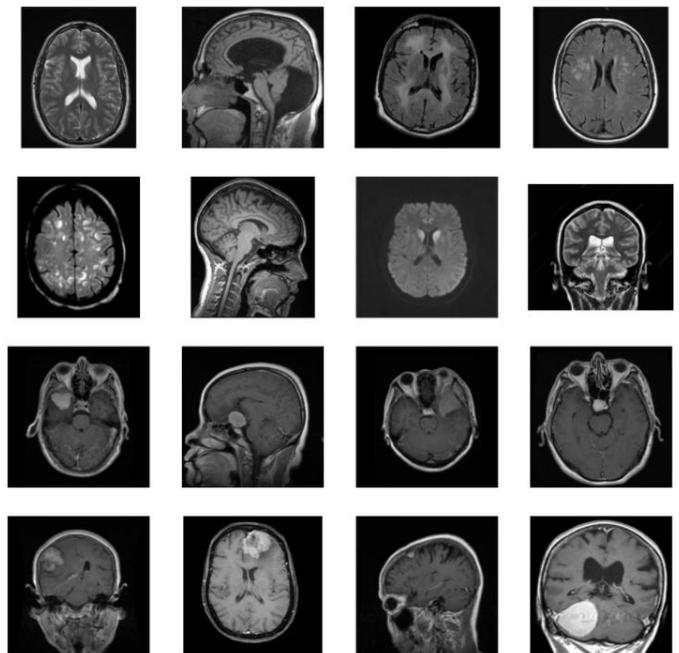


FIGURE 2. Data visualization from the given dataset, downloaded from Kaggle website, involving glioma tumor, meningioma tumor, and pituitary tumor

### *Data Preprocessing*

Since the size of the data is relatively insufficient to train a deep learning model, we had to multiply the data before putting it into the model and running it. For efficient data augmentation, we used Keras' ImageDataGenerator function. Through ImageDataGenerator, shear range, zoom range, horizontal flip, vertical flip, rotation

range, width shift range, height shift range, etc. can be adjusted. All images were divided by 255 for normalization, and 30% of the training set was used as the validation set.

### Convolutional Neural Network (CNN)

A Convolutional Neural Network (CNN) consists of a convolution layer, a pooling layer, and a fully connected layer. When CNN gets an input image, it first creates a convolution layer through a filter and produces a feature map, which is called a kernel. After that, the pooling layer reduces the size of the feature map by calculating the average or maximum value of the feature map. These are called max pooling and average pooling, respectively. A fully connected layer is the same as a deep neural network; the main purpose of this layer is to classify objects with activation functions. For multi-class classification, the softmax function is used as the activation function; for binary classification, the sigmoid function is mainly used [14].

### Pre-trained CNN

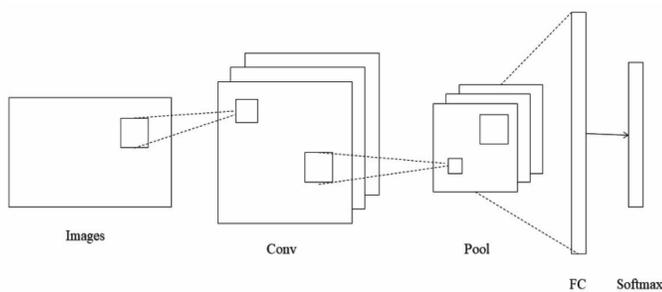


FIGURE 3. Overall architecture of the CNN for image analysis and classification

To extract features from images, we used pre-trained CNN models such as VGG16, VGG19, MobileNet, Inception-Resnet\_v2, and Inception\_v3. These pre-trained models can be downloaded from Keras and were pre-trained on a dataset named ImageNet. Because CNN layers such as pooling and conv layers are properly arranged and pre-trained with a large image set in advance, the accuracy is relatively higher than

that of training through a general CNN model. In particular, these models extract features of images to be employed by the user, and the layers to be classified after they are defined by the user [15].

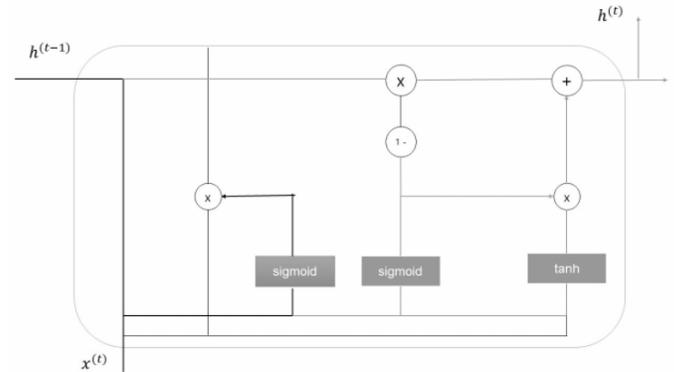


FIGURE 4. Overall architecture of the GRU

### Gated Recurrent Units (GRU)

$$z_t = (W_z[h_{t-1}, x_t] + b_z) \quad (1)$$

$$r_t = (W_r[h_{t-1}, x_t] + b_r) \quad (2)$$

$$h_t = \tanh(W_h[r_t \odot h_{t-1}, x_t] + b_h) \quad (3)$$

$$h_t = (1 - z_t) \odot h_{t-1} + z_t \odot h_t \quad (4)$$

In the case of LSTM, there were three gates: a forget gate, an input gate, and an output gate, but in the GRU, only two gates are used: a reset gate and an update gate. In addition, the cell state and hidden state are combined to express a single hidden state. The formula to find the reset gate corresponds to Equation (2) in the formula above. This is a method used to obtain the hidden state of the previous time and the  $x$  of the current time by applying the activation function sigmoid. The result will have a value between 0 and 1, which can be interpreted as information about how much to use the value of the previous hidden state. The value from the reset gate is not used as it is but is reused by expression (3). In equation (3), it is calculated by multiplying the hidden state of the previous time by the reset gate. The update gate plays a similar role to the input and forget gates of LSTM, and the key is to obtain the ratio of how much past and present information will be reflected. As a result of Equation (1),  $z$  reflects

how much current information will be used. And  $(1-z)$  reflects how much to use for past information. So, each role can be viewed as an input and forget gate of the LSTM, and finally, the hidden state of the output value at the present time can be obtained through Equation (4)[16].

### *Bidirectional GRU*

A sequence processing model called a Bidirectional GRU (BiGRU) consists of two GRUs. One takes the input from a forward direction while the other takes the input in a backward direction. It utilizes the bidirectional recurrent neural networks that only use input and forget gates in the entire process [17].

### *GradCAM*

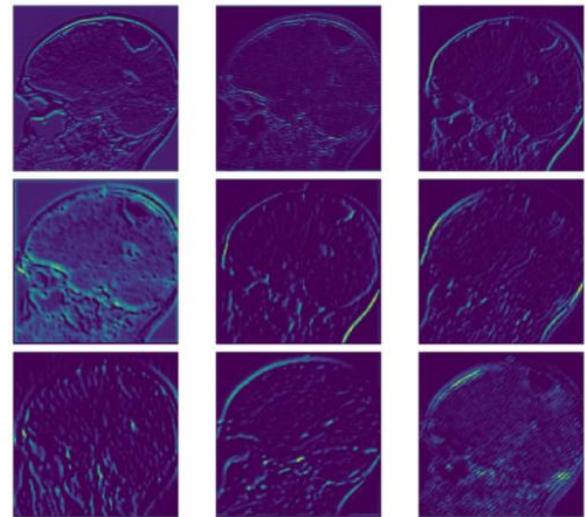
After classifying the pre-trained CNN models to obtain accuracy, Gradient-Weighted Class Activation Map (Grad-CAM) was used to check which part had abnormalities. Grad-CAM provides the cause for the classification result, and uses Global Average Pooling (GAP), instead of the fully connected layer used before final classification in the existing CNN model. It is shown through the heat map; the purple part indicates normal while the red indicates abnormal parts [18].

### *Proposed Model*

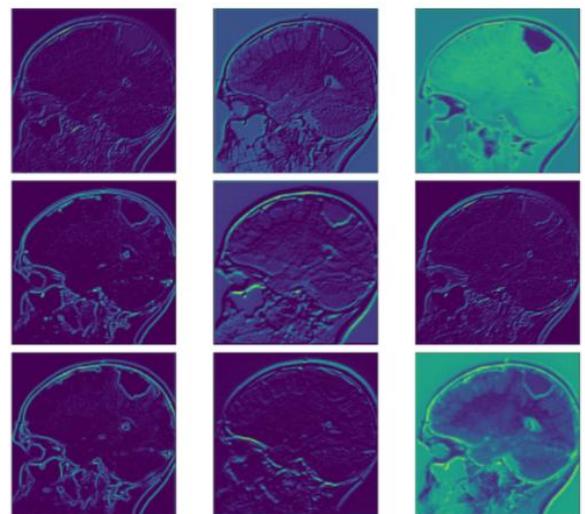
To improve classification accuracy, the Xception model - one of the pre-trained models - was used. In addition, bidirectional GRU was used for more accurate classification, contrasting with the existing models (in which a fully connected layer is added at the back of the model). Furthermore, a dense layer with 512 nodes was added as well as a dropout layer to prevent overfitting. The optimizer used nadam, the learning rate set at 0.001, and early stopping was set to stop training when the validation loss fell.

## **Results**

### *Visualization of Convolution layers*



According to the Figure 5, we could find that the first layer of CNN is to gather a collection of different types of edge detectors. Almost all of the information in the initial photo is preserved during this stage of activation. As the layers move up, activation becomes more abstract and visually difficult to understand. The representation of the upper layers shows less information about the visual content of the image but more information about the class of the image. In the first layer, all filters are active on the input image, but as layers move up, the filters become inactive. This means



that the pattern encoded in the filter did not appear in the input image.

This shows some of the important features that deep neural networks typically exhibit in learned

representations. The features extracted from the layer become more and more abstract along each depth of the layer. The activation of higher floors results in less and less visual information about a particular input, and more of a list of targets. Deep neural networks behave like a pipeline of information cleansing over the source data being inputted. Repetitive transformation filters out irrelevant information, and useful information is highlighted and improved.

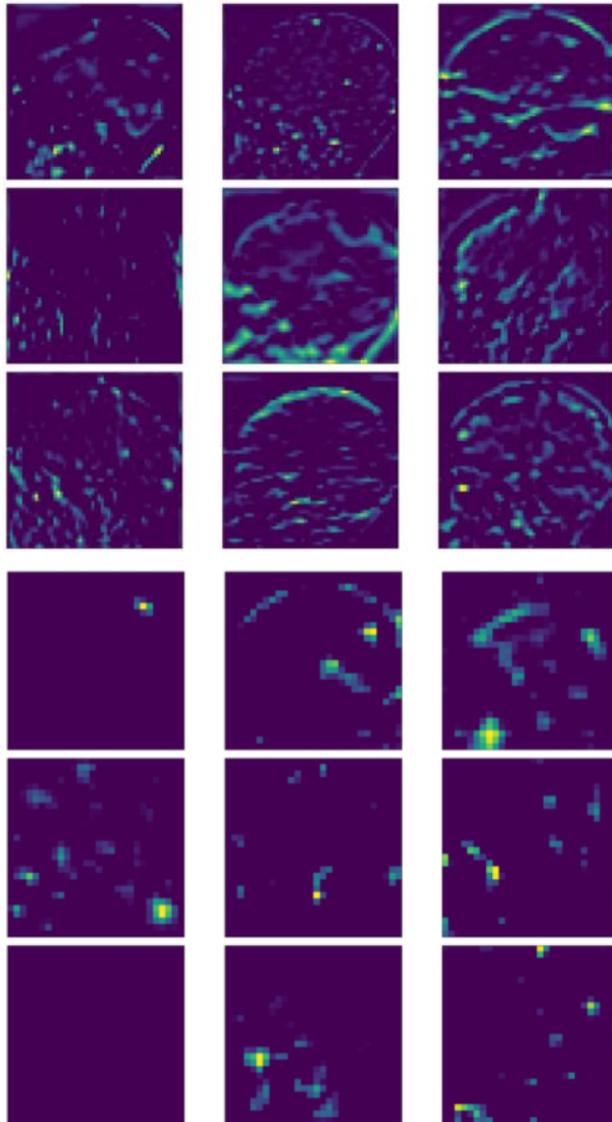


FIGURE 5. Visualization of the convolution layers; shallow layer to deeper layer

*Visualization of Pooling and Activation layers*

Convolutional layers were used to extract core features of an image and further use these distinct features to identify images that contained features of the same sort. In this run, we used 3 layers of CNN including Convolution, Activation, and Max Pooling. With these three layers, we started to see the network focus on regions such as the meningioma tumor in the actual brain. These types of features would allow the CNN through deep learning to differentiate between meningioma, pituitary, and glioma tumors. These neural networks are able to distinguish patterns in images that become akin to what the human eye can do, in focusing on one area and region to create a visual representation. According to the result from Figure 6, we could figure these processes through visualizing our dataset.

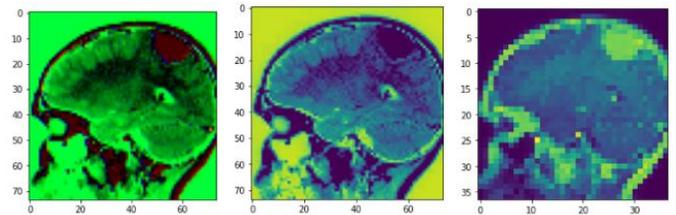


FIGURE 6. Visualization of the activation and pooling layers; shallow layer to deeper layer

*Accuracy of proposed model*

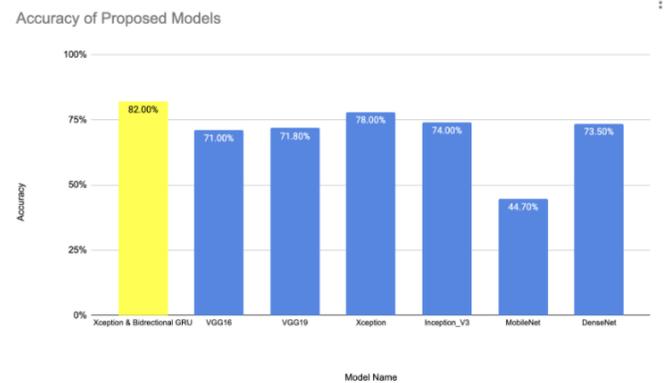


FIGURE 7. Graph for accuracy comparison; proposed model and other deep learning models including Xception + Bidirectional GRU, VGG16, VGG19, Xception, Inception\_V3, MobileNet and DenseNet

According to the Figure 7, our main proposed model of Xception + Bidirectional GRU, the accuracy was the highest with an accuracy of 82.00%. The model with the second highest accuracy was Xception with a 78.00% accuracy. In comparison, VGG 16 and VGG 19 were around the 71.00% accuracy range. The lowest model accuracy was 44.70%, coming from MobileNet. Inception\_V3 and DenseNet had similar accuracy percentages with 74.00% and 73.50% respectively. As the bidirectional GRU was implemented instead of fully connected layer for the classification, this replacement is believed to enhance the performance compared to the vanilla Xception model.

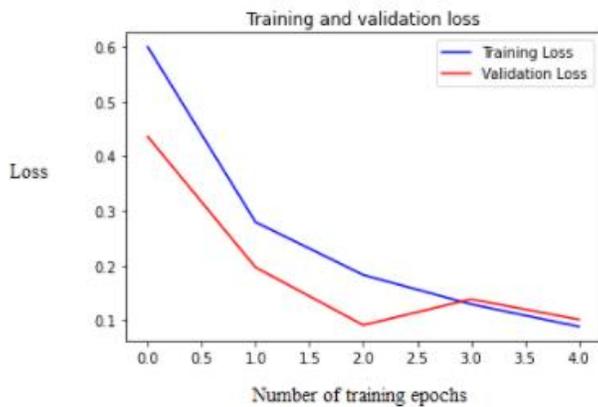
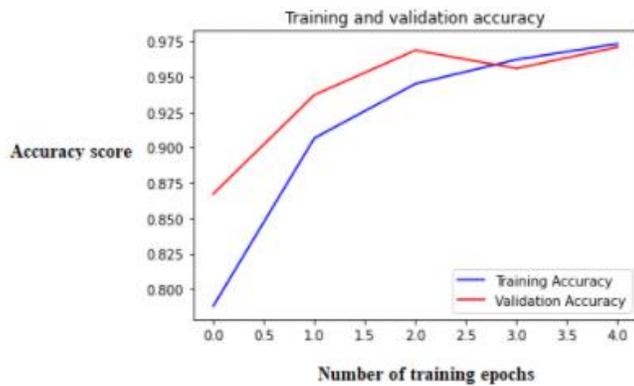


FIGURE 8. Graph for loss and accuracy from training and validation sets

Looking at the Figure 7 and Figure 8 above, it can be seen that during model training, the accuracy of the training set and the accuracy of the

validation set increased almost continuously, reaching about 97.5%. It is shown that the loss of the training set and the loss of the validation set also decreased continuously during model training. However, it was found that overfitting occurred because the accuracy in the actual test set was about 82%.

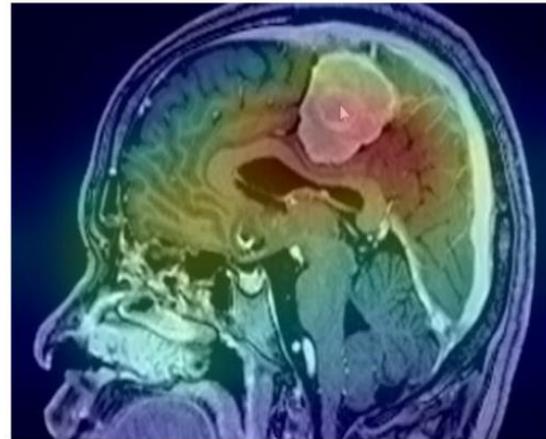


FIGURE 9. Visualizing anomaly parts of meningioma tumor via grad-CAM

As shown by the red heat mapping in this brain scan shown in the Figure 9, it accurately aligns with the part of the meningioma tumor, the white oval shaped tumor. This shows the validity in this proposed model used in utilizing heat maps.

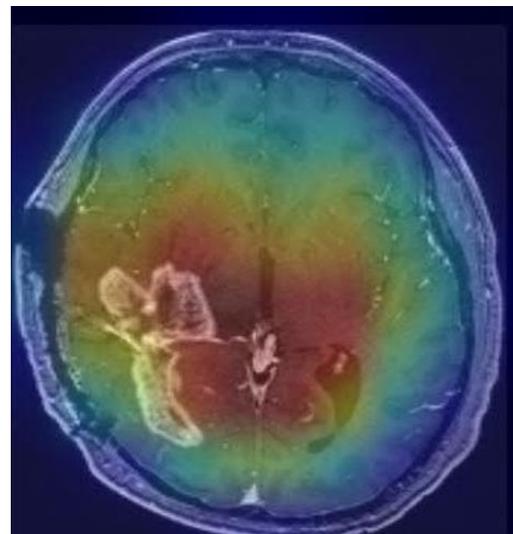


FIGURE 10. Visualizing anomaly parts of glioma tumor via grad-CAM

In this Figure 10, the glioma tumor can be seen as the white area, which the heat map was in the vicinity of. As this figure does not show the complete strength of the heat maps, this was one example of a weakness in this proposed model.

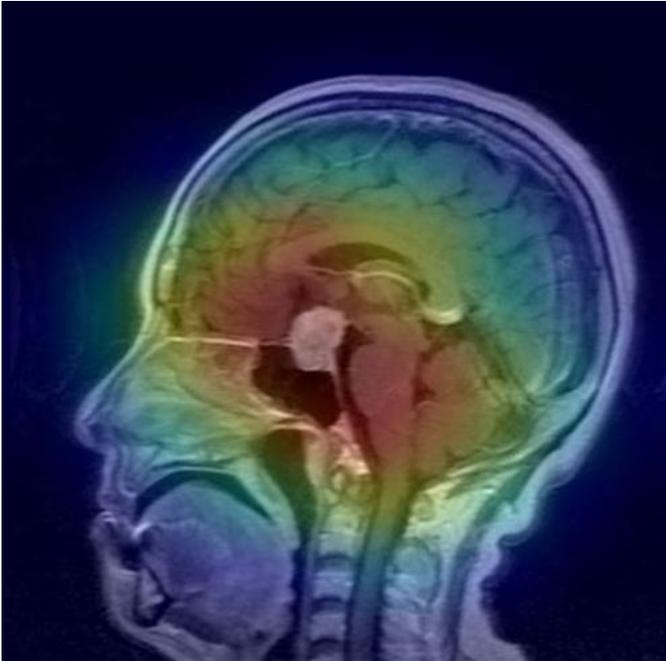


FIGURE 11. Visualizing anomaly parts of pituitary tumor via grad-CAM

In this Figure 11, the heat map centered in the area towards the pituitary gland, showing the efficacy of this proposed model. Although the gland itself is not opaquely visible, the heat map shows the suggested region.

## Discussion

### *Principal Finding*

A principal component to this research was the visualization of abnormal and malignant aspects in MRI Brain scans that was not seen in previous related works. By using heat maps to visualize the specific areas of tumors in the brain, comparisons can be drawn to the related works “Brain tumor classification using deep CNN features via transfer learning” and “Brain tumor classification using back propagation neural network”. Although these related works used similar techniques and applications to show results of

neural networking, they lacked the element of heat mapping and visualization that brings this research to another layer. This research was able to imply and underscore the similar steps of Convolutional Neural Networking to that of the human eye; As the features extracted from layers improved and became more abstract, the activation of higher floors became less about visual information and more about a list of targets.

### *Limitation*

Although this research was able to find key principal components of CNNs, there were also some limitations. One of these came from an accuracy that was not able to surpass 90%. This is seen as a limitation as it does not show reliable data throughout this neural network. A second limitation came from the fact that we used the simplest classification to network; in the computer vision field, classification, object detection, and segmentation are often 3 key factors, but we were only able to use classification as our data factor. Segmentation methods such as Unet and FCN (Fully Convolutional Network) were not utilized because we were unable to use a mask.

## Conclusion

Through continued analysis and research, we concluded that neural networking did follow a pattern that showed visualization of the human eye. As more layers of CNN were added, filters became inactive, and patterns encoded thus did not appear in input images. This showed that important features of deep neural networking exhibited learned representations. By using 3 layers of CNN, Convolution, Activation, and Max Pooling, these layers were able to focus on the actual regions of tumors in the brain. The proposed model of Xception + Bidirectional GRU thus had the highest accuracy of 82%.

Features and layers were an important step in this study as we found out activation of higher floors focused on making visual information a target-based system. However, further study is

necessary to prove this data to be valid and reliable, as limitations were that accuracy was less than 90% and we were only able to utilize classification as our data factor. In further studies, it is important to use a mask that would allow us to use segmentation and increase the accuracy of our proposed models to over 90%. Moreover, applying explainable AI technologies that could make AI decisions both understandable and interpretable by humans while maintain the performance could help humans to use deep learning technologies more efficiently.

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# Evaluating general ubiquitination techniques to find a method effective for AChR autoantibodies as a potential treatment of Myasthenia Gravis

Suhana Singh

Dougherty Valley High School, United States

suhanasingh270615@gmail.com

## Abstract

Myasthenia gravis (MG), a chronic autoimmune disease, affects about 20 out of every 100,000 thousand people globally (Medline Plus, 2020). Currently there is no cure, but the disease can be managed with a variety of methods, the most common options being immunosuppressant medications and surgeries. MG occurs when AChR, or acetylcholine receptors, are targeted by autoantibodies produced by the bodies' immune system. These receptors are membrane proteins found on skeletal muscles which are crucial in muscle contraction, and the damage to them causes weakness of muscles among other symptoms (Chaio, 2015). This novel literature review aimed to explore a treatment option that could target the unique autoantibodies that attack the patient's AChR specifically, rather than the entire immune system as immunosuppressants do. Synthetic ubiquitin tagging was researched, and studies related to ubiquitination were found and reviewed. The practicability of synthetically tagging desired proteins with ubiquitin to initiate proteolysis as a potential treatment for Myasthenia Gravis was then explored. A practical method was found to be able to implement in AChR autoantibodies for MG treatment.

*Key words: Myasthenia Gravis, auto-antibodies, immunosuppressants, ubiquitin, proteolysis*

## Introduction

### *Overview of Myasthenia Gravis*

Myasthenia Gravis is characterized as a chronic autoimmune disease. The most common symptoms include muscle weakness and fatigue (Mayo Clinic Staff, 2021). The disease is caused by autoantibody formation against the nicotinic acetylcholine postsynaptic receptors (abbreviated AChR) at the neuromuscular junction of skeletal muscles (Jowkar et al., 2018). The antibodies bind to the AChR and assemble a complex. An increased amount of calcium flows through this complex, called the membrane attack complex (MAC), and causes damage to the membrane of the receptor. This results in a less effective response to acetylcholine, a neurotransmitter that enables muscle contraction. This influx of calcium also causes damage to sodium channels, which increases the threshold that is required of muscle action potential (Phillips & Vincent, 2016). Essentially, the damage to these receptors results in the rapid fatigue of any muscles under one's voluntary control (Mayo Clinic Staff, 2021). The muscle fatigue varies over time, usually worsening with activity and improving in repose. A patient may experience symptoms such as drooping of the eyelids (ptosis), unusual facial expressions, difficulty holding up their head, speech impairment (dysarthria), chewing and swallowing problems (dysphagia), trouble lifting objects, trouble rising from a seated position, and breathing problems stemming from weakness in

chest wall muscles and the muscle separating the abdomen from the diaphragm, among other symptoms (Medline Plus, 2020).

### *Current Treatments*

Treatment of Myasthenia Gravis currently includes medications, surgery, and other therapies. Treatment plans differ with each patient and depend on age, severity of disease, which muscles are affected, and presence of other medical problems (Conquer MG, 2019). This study focuses on the medicinal aspect of treatment for Myasthenia Gravis. There are currently two types of medications used: anticholinesterases and immunosuppressants (Conquer MG, 2019). Anticholinesterases are drugs that inhibit acetylcholinesterase and butyrylcholinesterase (enzymes that break down acetylcholine), thus prolonging the existence of acetylcholine after it is released from nerve endings in the neuromuscular junction. Anticholinesterases give acetylcholine a competitive advantage over the autoantibodies that block the AChRs by allowing more time for rebinding to the receptors and increasing the amount of acetylcholine released (Nair et al., 2004). However, anticholinesterases only temporarily relieve symptoms as they do not directly address the abnormal immune system attack. In contrast, immunosuppressants suppress the entire immune system to prevent the formation of the AChR autoantibodies in the first place. Prednisone is a commonly prescribed immunosuppressant for many patients with Myasthenia Gravis, which acts by resembling natural hormones produced by the cortex of the human adrenal gland. Other commonly used immunosuppressants include azathioprine (Imuran), mycophenylate mofetil (CellCept), tacrolimus (Prograf), methotrexate, cyclosporine (Sandimmune, Neoral), and cyclophosphamide (Cytoxan, Neosar) (Conquer MG, 2019).

### *Disadvantages of Current Treatments*

Anticholinesterases interfere with the normal functioning of the central nervous system (CNS) and the peripheral nervous system (PNS) through the inhibition of acetylcholinesterase, which hydrolyzes acetylcholine (National Research Council (US) Panel on Anticholinergic Chemicals, 1982). Excess acetylcholine in the synapse can lead to adverse side effects such as muscle twitching, muscle cramps, and sweatiness (Conquer MG, 2019). Immunosuppressants can also have extremely serious side effects. Immunosuppressive drugs increase the risk of infection because they suppress the entire immune system rather than targeting the specific problem, resulting in suppression of both harmful and helpful antibody creation. The immune system is weakened and cannot fight off disease as efficiently (Conquer MG, 2019). The authors of one recent study, published in *Jama Open Network*, focused on the relation between severe COVID-19 symptoms or hospitalization and patients' use of drug-induced immunosuppression by medicines such as Prednisone. The study found that drug-induced immunosuppression could elevate the effects of COVID-19 if an immunocompromised patient was infected (Kenney, 2021). COVID-19 is just one disease of many that drug-induced immunosuppression leaves patients compromised to. In addition, Prednisone carries the risk of a multitude of possible side effects: insomnia, mood changes, weight gain, fluid retention, reduced resistance to infection, increased susceptibility to diabetes, high blood pressure, osteoporosis, glaucoma, cataracts, and stomach ulcers, along with other less common side effects (Conquer MG, 2019).

### *Rationale of Exploring Ubiquitin Tagging*

This article aims to identify a method of treatment for MG that could specifically target the unique autoantibodies rather than the entire immune system. Ubiquitination of AChR autoantibodies, a type of protein, is a potentially effective method to

treat Myasthenia Gravis to specifically target the immune system attack. Targeted proteolysis was chosen as the method of protein degradation for this project because of the ability to target specific proteins. Ubiquitination is involved in various fundamental cellular processes including protein degradation, gene transcription, DNA repair and replication, intracellular trafficking and virus particle budding. Protein ubiquitination is classified as a type of post-translational modification. Enzymes regulate the conjugation of ubiquitin, a small regulatory protein (Smith, 2018), to lysine residues of a target protein. Ubiquitin-activating E1 enzyme activity is subsequently followed by ubiquitin-conjugating E2 enzyme activity, which is then followed by ubiquitin-ligating E3 enzyme activity to initiate the ubiquitin-proteasome pathway. The system targets 80% of the proteins in a given eukaryotic cell for degradation (Chen et al., 2014). The hydrolyzation of ubiquitin-tagged proteins to their amino acids is catalyzed by the 26S proteasome, which is found in the nucleus and cytosol of all cells and constitutes approximately 1-2% of cell mass. The proteasome binds to the target protein by recognizing the ubiquitin tag (Lecker et al., 2006). The specificity of this system, by the tagging of the individual proteins, is what allows for the potential of a targeted treatment for the AChR autoantibodies.

## Research

### *General Research in the Field of Ubiquitination*

There have been multiple studies that have led to the creation of a synthetic ubiquitinated protein, however no research was found on evaluating the feasibility of creating a ubiquitinated AChR autoantibody. Therefore, multiple studies were analyzed to evaluate the effects of these experiments on other proteins, and then used to evaluate the practicability of using the same methods on an AChR autoantibody.

The following studies were analyzed to determine the process of ubiquitination, the type of protein ubiquitinated, and the results of the experiment.

### *Studies*

Study 1: Structure–Activity Analysis of Semisynthetic Nucleosomes: Mechanistic Insights into the Stimulation of Dot1L by Ubiquitylated Histone H2B (McGinty et al., 2008).

1. Process: A study published in *Nature* aimed to examine the effects of a chemically ubiquitinated histone H2B on hDot1L-mediated intranucleosomal methylation (McGinty et al., 2008). A peptide containing the residues 117-125 of histone H2B, including an A117C substitution, was synthesized. Recombinant ubiquitin (1–75)-alpha-thioester was also synthesized, and the two were linked using a ligation auxiliary consisting of two orthogonal amino-thiol handles. Photolysis was used to remove the ligation auxiliary. The protein was then linked to residues 1-116 of recombinant H2B. Another desulphurization reaction was used to convert cysteine to alanine in the product. This led to the creation of a mono-ubiquitinated histone H2B via lysine 120 (McGinty et al., 2008).
2. Protein Used: Histone H2B
3. Results: Tens of millions of grams of ubiquitylated protein were routinely generated. The product created included a G76A mutation, however found that it was indistinguishable from the native protein (McGinty et al., 2008).

Study 2: Highly Efficient and Chemoselective Peptide Ubiquitylation (Kumar et al., 2009).

1. Researchers were able to modify a lysine amino acid by adding thiol group directly on the delta carbon of the side chain (Drahl, 2009). The modified lysine, called  $\delta$ -mercaptolysine, was then used to modify lysine 6 on a model 17-residue peptide alpha-synuclein. The peptide was then synthesized and a protective group was removed. Following this ligation step, a desulphurization reaction occurred,

allowing for the thiol at the  $\delta$  carbon to be removed and converted to the unmodified lysine (Kumar et al., 2009).

2. Protein Used: alpha-synuclein
3. Results: The temporary thiol-handle using the  $\delta$ -mercaptolysine allowed for the ubiquitination of the 17-residue peptide with a 78% yield of isolated product (Kumar et al., 2009).

Study 3: Chemically ubiquitylated PCNA as a probe for eukaryotic translesion DNA synthesis (J. Chen et al., 2010).

1. Process: Researchers used chemically ubiquitylated PCNA (proliferating cell nuclear antigen; a homotrimeric, toroid-shaped protein) as a probe for eukaryotic DNA synthesis. The PCNA they aimed to attach a ubiquitin to was much larger than the histone H2B that McGinty et al. successfully ubiquitinated. In order to accomplish ubiquitination of the PCNA, the researchers created a mutant version of the PCNA (K164C PCNA) that had a cysteine in place of lysine in position 164, which retained normal activity of the wild-type PCNA. They activated the ubiquitin C-terminal carboxylate and then created a modified ubiquitin by introducing a unique thiol at the C-terminus. The team treated it with a water-soluble reagent (5,5'-dithiobis-(2-nitrobenzoic acid)), thus facilitating the formation of a bond between the cysteine in the K164C PCNA and the modified ubiquitin. (J. Chen et al., 2010).
2. Protein Used: PCNA
3. Results: 4.5 mg of chemically-ubiquitinated PCNA was created with a yield of 80%, although not by a native isopeptide bond.

Study 4: A Pyrrolysine Analogue for Site-Specific Protein Ubiquitination (X. Li et al., 2009).

1. Process: By using a pyrrolysine analogue, X. Li et al. were able to demonstrate that it is possible to create a ubiquitinated protein in one ligation step from two genetically encoded segments (X. Li et al., 2009). They used a cysteine-containing analogue of pyrrolysine and incorporated it into position 21 of a calmodulin protein. Subsequently, they reacted that protein with a modified ubiquitin to create a semisynthetic ubiquitinated protein (H. Chen et al., 2018).
2. Protein Used: Calmodulin (CaM)
3. Results: 30% yield of recombinant CaM was ubiquitylated.

Study 5: Traceless and Site-Specific Ubiquitination of Recombinant Proteins (Virdee et al., 2011).

1. Process: Researchers were successful in forming a completely natural isopeptide bond between ubiquitin and a SUMO protein using site-specific incorporation of  $\delta$ -thiol-l-lysine and  $\delta$ -hydroxy-l-lysine into recombinant SUMO proteins. They used a pyrrolysyl-tRNA synthetase to link the ubiquitin to a specific lysine that they created in the recombinant protein. They used a series of protection and deprotection steps to create this isopeptide bond (Virdee et al., 2011).
2. Protein Used: SUMO Protein
3. Results: Formed completely natural isopeptide bond in mono-ubiquitinated SUMO proteins.

TABLE 1: Summary of Application of Study Methods to AChR Autoantibodies

Study	1 (McGinty et al., 2008)	2 (Kumar et al., 2009)	3 (J. Chen et al., 2010)	4 (X. Li et al., 2009)	5 (Virdee et al., 2011)
Practical for MG Treatment	No	Yes	No	No	No
Reason	Multistep Synthesis; AChR autoantibodies contain native cysteine	Efficient; Scalable; Can use protection on native cysteines using this method; Can be used for large proteins	Multistep synthesis; unstable bond between ubiquitin and protein	Incorporation of unnatural amino acid; Hard to scale, Protein used in experiment is significantly different than AChR autoantibody	Multistep synthesis, poorly soluble

## Discussion

Each study was successful in creating a ubiquitinated protein. In analyzing the data, it can be concluded if the method could be applied to ubiquitination of AChR autoantibodies. The discussion is as follows:

Study 1: This study used a multistep synthesis process that may be hard to recreate in labs. This poses an issue for the use of this method to produce ubiquitinated AChR autoantibodies- the process would need to be scaled up significantly to treat MG in a patient, and the multi-step synthesis could make that difficult. This experiment also relied on the fact that the histone H2B had no native cysteines (Faggiano & Pastore, 2014). However, AChR autoantibodies do contain cysteine, according to their FASTA sequence (NCBI). Since this study provides no method to ubiquitinate proteins containing native cysteines, this method of ubiquitination is not practical for use in MG treatment.

Study 2: This study provides a model that, in principle, could be used in sequential ligation for the synthesis of ubiquitylated proteins. It is highly efficient, which is necessary in order to be able to scale up to treatment. However, the study has two

downfalls. One is that it uses a 17-residue model peptide, and claims that in order to achieve synthesis of a ubiquitin to a full-length protein, there will need to be a second ligation step to attach the ubiquitin-ligated peptide with the rest of the peptide. In doing this, one must use a protective group to protect the N-terminal cysteine or the  $\delta$ -mercaptolysine. The second downfall is that the method works without the presence of other cysteine residues, while the AChR autoantibody contains cysteine residues. However, this problem could be overcome by using temporary protection of the native cysteine, therefore rendering this method a possible effective process to use to ubiquitinate AChR autoantibodies.

Study 3: This protein was similar to the AChR autoantibody in that it is large, and the lysine site of ligation was distant from both ends of the peptide. However, this process requires multistep synthesis and is hard to accomplish, therefore making it difficult to scale up in treatment. One benefit to this treatment is that the PCNA contained native cysteines, similar to the AChR autoantibodies, that were mutated to serines. Yet, in the presence of reducing agents, the ligation is cleaved very quickly, within 10 minutes, therefore making this method very unstable.

Study 4: Incorporating an unnatural amino acid worked in this experiment, however without testing it is not possible to know if incorporating an unnatural amino acid will alter the ability of proteases to recognize a ubiquitin tag on an AChR autoantibody. It is also difficult to synthesize the amount of the unnatural amino acid that would be needed for effective treatment of a patient. CaM is also a significantly different protein than the AChR autoantibody. The ubiquitin doesn't mark CaM for degradation, but rather helps monitor its regulatory activities. Although this study provided a method to synthetically attach ubiquitin to a desired protein, it will not be effective for our purposes.

Study 5: This method requires multistep synthesis, including multiple protection and deprotection steps, which can become difficult while scaling up to creating many ubiquitinated proteins, which would be necessary in using ubiquitination techniques to target AChR autoantibodies. However, Virdee et al.'s method of producing a native peptide bond eliminated the use of denaturing buffer conditions, which allowed for the bonds to hold for longer. However, due to the fact that the bond is poorly soluble, it becomes difficult to break down.

## Conclusion

By analyzing the studies, it is clear that a few problems arise when trying to apply current ubiquitination methods to AChR autoantibodies. Three major ones are that first, AChR autoantibodies contain native cysteines, which interferes with many of the methods proposed. Second, to be able to implement ubiquitinated AChR autoantibodies, many of these processes would need to be scalable to create enough product to treat disease in a human patient. Third, AChR autoantibodies are much larger than the majority of proteins used in these experiments. The only study that addresses all of these concerns is Study 2: Highly Efficient and

Chemoselective Peptide Ubiquitylation (Kumar et al., 2009). It is scalable due to the efficiency of the method that significantly reduces the amount of time needed. It also proposes a solution for ubiquitinating proteins with native cysteine residues, such as the AChR autoantibody, by proposing the use of a temporary protection auxiliary for the native cysteines while the ligation occurs. In terms of size of the protein, the study indicated that this method could be used in two ligation steps to be able to ubiquitinate a full-length protein. Therefore, this method for ubiquitination of target AChR autoantibodies could be used to create a potential treatment for MG.

It is necessary for this method to be tested in a laboratory to assess the methodology. However, by narrowing down the methods that are appropriate for testing in MG treatment, this article aims to improve on current treatments and provide a clear pathway for the future of AChR autoantibody degradation in MG treatment.

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# From Pagodas to Printed Homes: Exploring the Flexural Strain, Deflection, and Relative Strength of 3D Printed Japanese Joinery

Kevin Slattery

The American School in Japan, Japan  
22slatteryk@asij.ac.jp

## Abstract

Large-scale 3D printing, a recent technological advancement, is a cost-efficient and eco-friendly method of construction. However, its products suffer from poor aesthetics, which drive away many potential buyers. Refraining from using any nails, screws, and adhesives, traditional Japanese joints truly depict the beauty of Japanese nature. The application of traditional Japanese joinery may solve the poor aesthetics of large-scale 3D printed structures. Furthermore, these joints are historically earthquake resistant and may improve the safety of 3D printed structures against natural disasters. This study explores the potential uses and limits of 3D printed Japanese joinery when applied to large-scale structures. Four traditional joints were 3D printed using Poly Acetic filament (PLA) at 10 % infill. Three-point flexural tests were analyzed using digital image correlation (DIC) to determine each joint's strain to failure, deflection, and relative strength. The Kanawa Tsugi joint had a significantly higher flexural strain than the other joints tested. Moreover, there were various statistical differences observed among deflection measurements of each joint. 3D printed Japanese joinery could be applied for quick assemble purposes, such as for building formwork.

*Keywords: Japanese Joinery, Flexural Strain, Deflection, 3D Printing, Digital Image Correlation*

## Introduction

Traditional Japanese carpentry is a form of wooden architecture and joinery that originated around 1400 years ago during the Asuka era (宮大工の歴史, 2021). The work of Japanese carpenters, known as the Daiku, mainly revolves around visual aesthetics that spotlight the theme of Japanese nature. The Daikus' refrain from using any nails, screws, or glue to connect joints allows the creation of a natural look that results in a visually pleasing product. The works of the Daiku are seen in shrines, temples, and pagodas throughout Japan. Traditional Japanese carpentry is also seen in residential structures, which are performed by the Sukiya-Daiku (数寄屋大工).

Although Japan is an earthquake-prone nation, before the Meiji Restoration (1868), Japanese carpenters did not focus on earthquake-proof architecture. Instead, the focus of the Miyadaiku was on the visual aesthetics of their final product. According to Clancey (2006), as foreign engineers began to observe the structural flaws of Japanese architecture, Daikus faced the dilemma of having to favor either aesthetics or improve the structural integrity in their work. Scottish civil engineer RH Brunton, who the Meiji Government hired in 1868, criticized the ways of Miyadaiku carpentry as "unfit to earthquakes due to its unnecessarily heavy roof and weak framework."

Brunton described Japanese architecture as “worst adapted to withstand heavy shock” (Clancey, 2006). The foreign criticism of Japanese carpentry led to a shift in the Daikus’ focus. They incorporated aspects of western technology such as diagonal braces and iron fittings within Japanese frames. This helped improve the rigidity and strength of Japanese structures, significantly improving protection against earthquakes.

*Importance of Joinery to Earthquake Resistance*  
Even without Western technology, Japanese pagodas built centuries ago are earthquake-resistant. One example of this is the Five Storied Pagoda at Horyu-Ji, a wooden pagoda built in the year 607. The Five Storied Pagoda (Goju-no-to) at the Horyu-Ji temple is the oldest pagoda in Japan. Since the pagoda was initially built, the Goju no To has experienced earthquakes with magnitudes greater than 7.0 at least forty-seven times (Horyuji: A Brief History). Yet, the beautiful pagoda still stands today. Theories attempting to explain the earthquake-resistant characteristic of pagodas have long been debated.

The initial theory explaining this phenomenon focused on the pagoda’s vibrational period. The approach was that the structure’s naturally long vibrational period is well-matched to the seismic frequency of the ground during an earthquake, allowing the pagoda to “slide” in a flexible manner at the approximate frequency of the accelerating ground waves (Majima, 1927). According to this theory, the matching vibration of the ground and the pagoda allows resonance and minimal stress throughout the structure. However, measurements have shown a significant difference in the natural period of the pagoda and the average period of ground acceleration during an earthquake. The period of the pagoda is far longer than that of the ground acceleration. Therefore, the possibility of resonance with ground acceleration waves causing this phenomenon is minimal. Thus, the “ground wave

resonance” theory does not serve as an explanation of the pagoda’s structural resistance to earthquakes (Tanabashi, 1960).

A new theory was formed to replace the “ground wave resonance” theory. This theory focused on the shin bashira, the central wooden column of the pagoda.

During the early stages of seismic study in Japan, the structural purpose of the shin bashira was not well understood by Japanese architects since the concept of the shin bashira was passed through the Korean Peninsula carrying Chinese and Indian roots. The shin bashira is not a Japanese innovation (Ooi, 2012). Japanese engineers developed the “Pendulum Theory” to explain the structural purpose of the Shin-Bashira. The theory states that the shin bashira sways in the opposite direction of the mainframe during an earthquake, resulting in movements to “counteract” each other. This results in less stress applied to the overall structure. However, this theory is not accepted today due to the discovery that the shin bashira does not directly play a role in protecting the tower, but rather the joints and connections that surround it do (Abe, 2018).

The seismic resistance of pagoda structures can be described through 3 characteristics made possible by the wooden joinery surrounding the shin bashira.

1. Ability to withstand large lateral loads.
2. High deformation limit until complete failure of the structure.
3. A large amount of structural damping.

Pagodas are capable of undergoing a large amount of plastic deformation before failure: a permanent distortion resulting from high load or stress. A pagoda with considerable lateral strength throughout its body and a large limit of lateral deflection indicate that a large amount of potential energy can be stored before the structure’s complete failure (Tanabashi, 1960).

Today it is accepted that the frictional damping of traditional Japanese joinery within the pagoda provides earthquake resistance. The frictional damping provided by each joint is key to an earthquake-resistant structure (Nakahara, 2000). These joints that connect the shin bashira to the outer wooden columns allow for a flexible “spine-like” support that efficiently absorbs seismic stress caused by the earthquake (Hanazato et al., 2004).

The seismic performance of flexible traditional Japanese joinery is seen not only in pagodas but also in other Japanese structures. According to Yamada (2004), “Traditional Japanese wooden buildings are typically composed of wooden frames with joint connections and plaster walls to enclose the buildings and separate rooms”. In modern wooden houses, the walls and braces play essential roles in resisting earthquakes. With the use of traditional Japanese joinery, structures are strong and flexible. Similar to the structure of a pagoda as a whole, Japanese joints have a high deformation limit. These characteristics of traditional Japanese joinery play into the damping of the structure. The frictional damping of each wooden joint in the structure allows for absorbing stress that protects the structure from collapse (Nakahara et al., 2000).

Among traditional Japanese joinery, a few stand out for their structural performance as well as aesthetics.

*Types of joints*

**Kanawa Tsugi (金輪継):**

The Kanawa Tsugi is considered one of the strongest traditional joints and is used to connect columns, beams, and girders because it provides strength in all directions. The joint is made of two identical pieces with a staggered pattern, fixed by a draw pin inserted in the joint’s midspan (Sumiyoshi, 1989).

**Koshikake Aritsugi (腰掛蟻継)**

The Koshikake Aritsugi is called the sitting-ant joint due to its trapezoidal shape that looks like the head of an ant. The Koshikake Aritsugi is placed horizontally within the frame and is the strongest in the perpendicular axis. However, the Koshikake Aritsugi is most commonly used in groundsills throughout Japan (Sumiyoshi, 1989).

**Kama Tsugi (鎌継):**

The Kama Tsugi, similar to the Kanawa Tsugi, is the most common joint used in structural application. The Kama Tsugi is often used in beams and girders. Furthermore, the complex shape of the Kama Tsugi results in a stronger joint than the Koshikake Aritsugi, especially in the perpendicular direction (Sumiyoshi, 1989).

**Shiho Kamatsugi (四方鎌継):**

The Shiho Kamatsugi, also known as the “impossible joint,” requires skillful craftsmanship to fabricate. Each piece is inserted in the oblique direction (45 degrees), which allows for an identical gooseneck motif to be found on all joint faces. The joint is primarily used to demonstrate the beauty of traditional Japanese joinery, and its application within structures is minimal (Sumiyoshi, 1989).

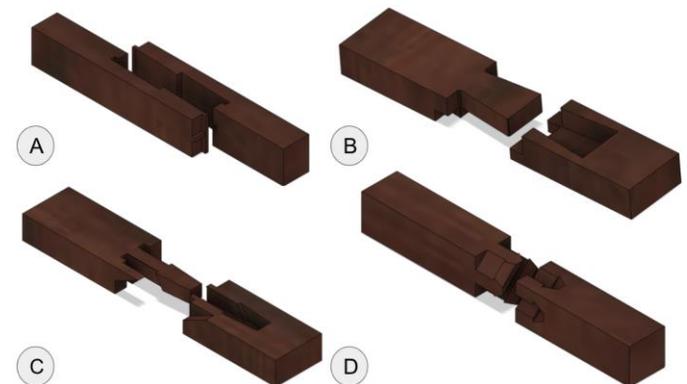


FIGURE 1: CAD representation of Kanawa Tsugi (A), Koshikake-Aritsugi (B), Kama Tsugi (C), Shiho-Kamatsugi (D)

### *3D Printed Structures*

AM, which stands for additive manufacturing, describes construction methods that involve adding layer-upon-layer material. Much of the recent AM construction developments focus on large-scale printing systems, such as the commercial 3D printed housing system by ICON. To reach the goal of commercializing sustainable housing that takes “half the time” to build and “half the price” to buy, 3D printed housing has become a new technology on the rise (ICON: Becoming Iconic). A cementitious filament is used to print these houses. An initial concern with the concept of 3D printed housing was its ability to withstand natural disasters. However, the cementitious material has been tested to be quite durable against natural threats. ICON has tested its cementitious material to be compressed to 6000+ psi, making it far more durable than wood (ICON: Becoming Iconic). Furthermore, wood is susceptible to weathering and damage over time, whereas cement is more resistant to aging issues such as mold.

3D printed housing is cheap, environmentally friendly, and, most importantly, structurally safe. However, a significant issue of 3D printed housing now lies within its design. 3D printed housing is currently not visually appealing to most. This is where traditional Japanese joinery could play a role in the future of 3D printed structures. 3D printed Japanese joints could be applied to 3D printed housing in the future to provide the visually pleasing natural aesthetics of a wooden house while maintaining sufficient structural stability and support against earthquake threats, especially in nations such as Japan.

### *Research Purpose*

The purpose of this study is to explore the potential uses of 3D printed traditional Japanese joinery in structural applications, focusing on its unique ability of earthquake resistance. A three-point flexural test of each joint will be analyzed to determine whether the joints are possible for an

application at a larger scale. The strain to failure, deflection, and relative strength of each joint will be analyzed and compared.

### **Methods**

The Autodesk Fusion 360 software was used to create the four traditional joints shown earlier (Kanawa-Tsugi, Koshikake-Aritsugi, Shiho-Kamatsugi, and Kama Tsugi). Autodesk Fusion 360 is a 3D computer-aided design software. On Fusion 360, each joint was scaled to a width of 12.5 millimeters. Furthermore, each connection was designed with a 0.5 mm offset so that pieces could interconnect smoothly without the need for excessive sanding. After each model on Fusion was converted to a .stl file, the joints were 3D printed at a 0.4 mm nozzle size. The common polylactic acid (PLA) filament was used to fabricate each joint, with a percent infill of 10%. PLA was used in this study due to its high availability. However, PLA is biodegradable and unreliable when applied to structural purposes (Kawashima, 2021). Yet, this study does allow testing of different joint configurations and their relative characteristics under a load.

### *DIC (Digital Image Correlation)*

Digital Image Correlation (DIC) was used to analyze each joint’s deformation and strain when countering a load. DIC allows for a full field strain and displacement analysis of the measured specimen. Frame by frame images of the specimen was taken by the test camera at regular intervals. DIC measurement could then allocate each pixel of the image to a coordinate. The changes in the stochastic pattern on the surface of the specimen within each frame allowed the DIC software to compute strain and displacement at each specific coordinate point (Sun, 2021). The GOM Correlate software was used in this study to analyze DIC measurements (GOM Metrology).

### *Joint preparation*

Each joint was cleaned so that there was no oil on the joint surface, allowing for optimal

measurements. Before applying a stochastic pattern, the joint surface was primed with a layer of white paint, allowing for better contrast with the pattern throughout the filming process. Using black spray paint, a stochastic pattern was applied on the joint surface so that the deformation of the surface could be analyzed on GOM correlate. A stochastic pattern is necessary for GOM Correlate to analyze surfaces, as the changes in the pattern must be computed to



FIGURE 2: Stochastic pattern applied to Koshikake-Aritsugi joint via black spray paint.

produce strain and deformation values (GOM Metrology).

### Setup

Each joint was held stable between wooden columns using clamps. The joints were firmly clamped in place at two contact points. There was one camera placed parallel to the joint, facing the connection. Another clamp was attached to the midspan of the joint. This is the third contact point, where the middle clamp will be tightened until failure of the joint is observed.



FIGURE 3: Experimental Setup

### Data Collection and Processing

The GOM software generated a strain field, in which the degree of strain throughout the joint surface was analyzed as a function of time. All measurements of strain were calculated by the quotient of the change in length and the reference length. This is called the technical strain. The strain to failure was recorded for each joint. Strain to failure, also known as flexural strain, is the nominal fractional change in the length of an element of the outer surface of the test specimen at midspan, where the maximum strain occurs. Moreover, vertical displacement of the joint was measured as well. The vertical displacement, also known as deflection, measures the maximum displacement on the joint's surface before reaching failure. Although the load was not measured in this study, the relative strength for each joint was recorded. The number of clamp rotations necessary to make the joint reach failure was recorded. The number of rotations correlates to the load applied to the joint.

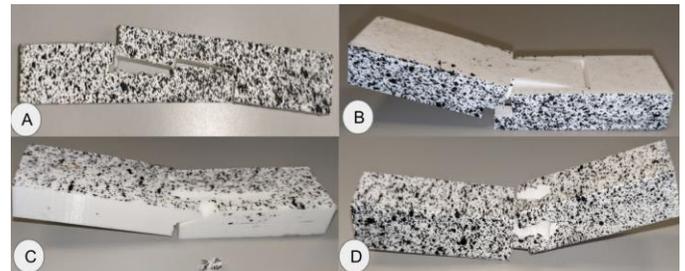


FIGURE 4: Joints after testing: Kanawa Tsugi (A), Koshikake Aritsugi (B), Kama Tsugi (C), Shiho Kama Tsugi (D)

Furthermore, the significance of data was analyzed with a statistical method known as one-way ANOVA (one-way analysis of variance). The one-way ANOVA tests whether the difference between means of samples is statistically significant. Tukey's honestly significant difference test (HSD) was used to determine which means were statistically different.

## Results and Discussions

### *Overview of PLA material*

Overview of PLA material PLA is a glassy polymer characterized by its high stiffness and non-crystalline structure (Lee, 2019). Therefore, PLA materials have a poor elongation at break. The flexural strain of PLA materials at 23 degrees celsius ranges from 0.5 to 9.2 percent. (Lanzotti, 2015).

### *Three-point flexural test results*

#### Kanawa Tsugi:

The Kanawa Tsugi experienced an average flexural strain of 21.6 % before failure, exceeding the flexural strain's estimated limit for PLA materials. However, the Kanawa Tsugi performed poorly in terms of deflection and strength. The low deflection limit of the Kanawa Tsugi seems to be caused by its strain distribution. As seen in Figure 6A, the configuration of the Kanawa Tsugi results in strain being concentrated at a singular point. Therefore, the joint suddenly reaches a high strain value (FIG 5A Top) before failing at a relatively small load. Furthermore, the Kanawa Tsugi had an average deflection of 1.97 mm, which is relatively low among the joints tested. The deformation of the joint before failure is low, causing the Kanawa Tsugi to undergo brittle failure. Lastly, the Kanawa Tsugi failed at an average of 2.7 rotations of the clamp. This makes the Kanawa Tsugi the weakest joint tested, failing at the smallest load.

#### Koshikake Aritsugi:

The Koshikake Aritsugi experienced an average flexural strain of 1.28 %, the lowest among the joints tested. As seen on FIGURE 6B, the high strain was concentrated at the engagement point between the two pieces. Furthermore, the joint experienced an average deflection of 3.2 mm. As seen in Figure 5B, the joint reaches a peak in the strain at approximately 30 seconds into testing (when the failure occurs). The failure of the Koshikake Aritsugi was not as sudden as the Kanawa Tsugi but was still brittle due to its

relatively low plastic deformation (deflection) before failure. The joint failed at an average of 5 rotations of the clamp, which places the Koshikake Aritsugi as the second strongest joint tested in terms of strength.

#### Kama Tsugi:

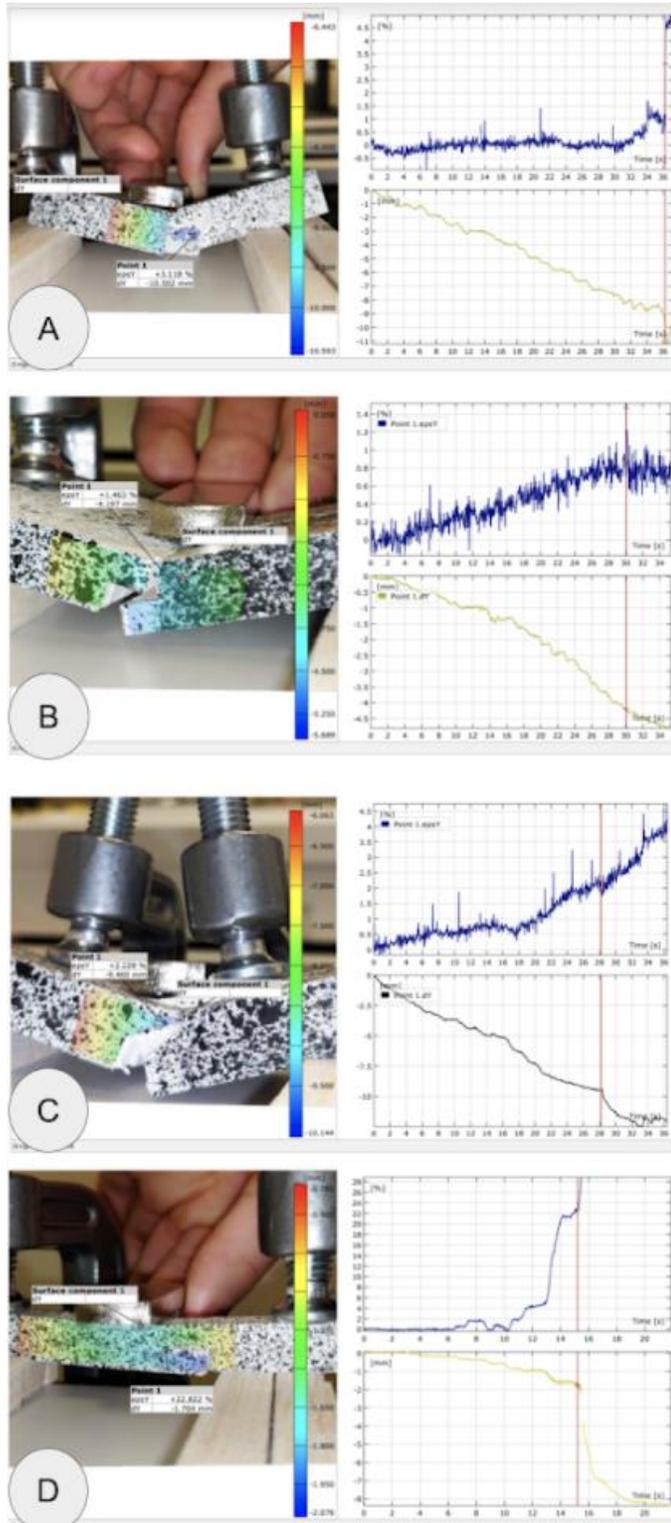
The Kama Tsugi experienced an average strain of 2.2 %. As seen on FIGURE 6C, the strain was relatively evenly distributed throughout the surface. Furthermore, the Kama Tsugi experienced a rather large deflection, with an average of 7.9 mm. As seen on FIGURE 5C, the joint failure occurs approximately 28 seconds into testing, where there is a sudden change in the displacement vs. time graph slope. At this point, the joint has already undergone significant plastic deformation. A relatively large deformation indicates a ductile failure. The joint failed at an average of 5.3 rotations of the clamp, making the Kama Tsugi the strongest joint tested.

#### Shiho Kama Tsugi:

The Shiho Kama Tsugi experienced an average flexural strain of 3.56%. As seen on FIGURE 6D, strain is concentrated on the gooseneck of the joint. The strain is concentrated at the gooseneck, which is a thin piece of the joint. Furthermore, the Shiho Kama Tsugi experienced the largest deflection among the joints, with an average of 9.2mm. Although the joint underwent a sudden failure, the failure is considered ductile due to the relatively large amount of deformation endured by the joint. Lastly, the joint failed at an average of 3 rotations of the clamp, making the Shiho Kama Tsugi a weak joint.

One-way ANOVA tests for flexural strain and deflection were significant ( $p \ll 0.001$  for each). The post-hoc Tukey HSD test revealed that the Kanawa Tsugi had a significantly greater flexural strain than the other joints tested ( $p = 0.001$ ). Furthermore, the Tukey HSD test revealed significant differences between the deflection measurements of the Kanawa Tsugi & Kama

Tsugi ( $p=0.001$ ), Kanawa Tsugi & Shiho Kama Tsugi ( $p=0.001$ ), the Koshikake Aritsugi & Kama



Tsugi ( $p=0.002$ ), and the Koshikake Aritsugi & Shiho Kama Tsugi ( $p=0.001$ ).

FIGURE 5: Displacement Mapping (left), Displacement vs. Time graph (top), Vertical Strain vs. Time graph (Bottom): Kanawa Tsugi (A), Koshikake Aritsugi (B), Kama Tsugi (C), Shiho Kama Tsugi (D)

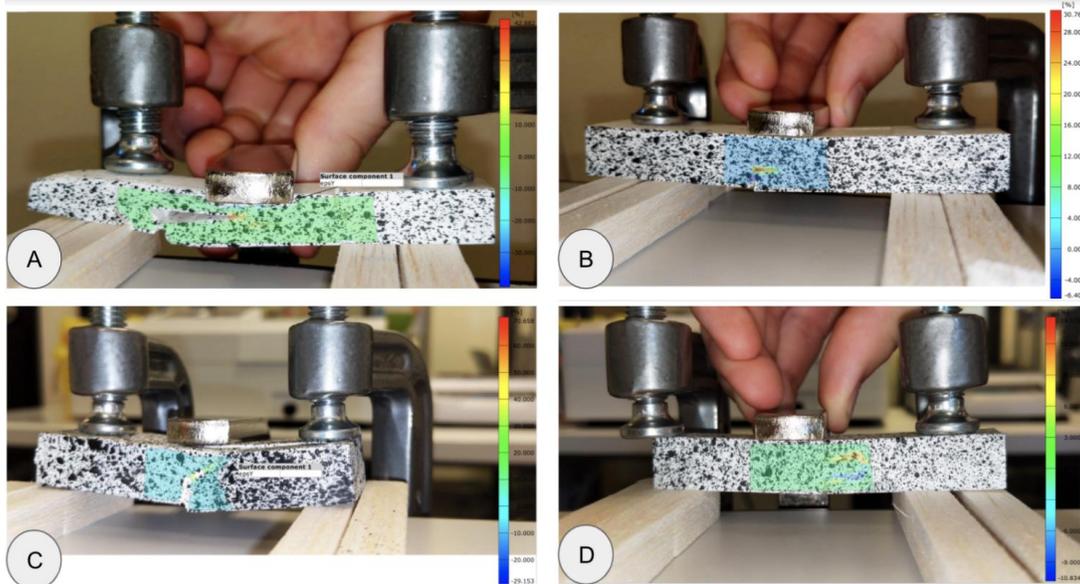
*Potential error and inaccuracy*

Since each connection is separated with a 0.5 mm gap, the displacement measurement for each joint does not only measure the deformation of the joint but also includes the distance of the movement of the upper piece until it makes contact with the bottom piece. This results in each measurement being approximately greater than the actual deformation limit of the joint.

*Comparison to real-world applications*

Consider L to be the distance between the two place-holder clamps for each test. Using the scale function on GOM Correlate, length L was measured. For beams in building construction, the max deflection allowed for serviceability is typically on the order of  $L/240$  or  $L/360$  (American Society of Civil Engineers, 2017). Therefore, the deflections exhibited in all tested joints do not meet serviceability limits in current building codes. However, instead of being applied within a structure, these joints could potentially serve as an option for formwork to reduce assembling and disassembling time.

The strain to failure of concrete beams in structural use is 0.004% and 0.02 % for standardized steel (Sun, 2021). The strain to failure of these commonly used materials in construction is nominal compared to the recorded measurements of each joint. However, the material difference must be considered. PLA filament is a naturally more flexible material than steel or concrete, and further research is necessary to correlate strain data for PLA material to standard codes used for construction.



### For future study

Although all joints used in this study are made with 10 percent infill PLA, joints may respond differently to the same load when made with different percent infills. Finding the optimum percent infill for structural performance could be the focus of a future study.

Furthermore, wood PLA, which is commercially available and relatively inexpensive, could potentially be an alternative for PLA when producing “wood-like” joinery. The powered wood within the filament creates a “flexible” material that might be better suited for Japanese joinery. The effect of different filaments should be further explored.

The Kanawa Tsugi especially should be further investigated due to its ability to withstand high strain limits, which could be helpful in structural applications. The high strain limit of the joint, which is a result of its high deformation limit, correlates to the earthquake-resilient properties of the joint. Further testing with the GOM ARAMIS program would allow an in-depth study into the flexural properties of the Kanawa Tsugi.

Through this study, I hope to have expanded future research about the applications of traditional Japanese joinery in settings that would

help improve both the visual aesthetics and the structural integrity of the structure.

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# Evaluating candidate IRAP inhibitors in *Ginkgo biloba* extract and their potential for cognitive enhancement

Napoleon Star

Institut Le Rosey

napoleonskystar@gmail.com

## Abstract

*Ginkgo biloba* is commonly used as an alternative medicine and is known for its nootropic effects. It contains many secondary metabolites, including terpene lactones and flavone glycosides. However, the molecular mechanisms of its cognitive enhancement are not well understood. Inhibition of Insulin regulated aminopeptidase (IRAP) has been shown to improve memory in previous studies. Here, we aim to compare the binding affinities of bioactive molecules in *Ginkgo biloba* extract to known IRAP inhibitors. Using an in silico approach, we found that Ginkgolide B had a similar result to AngIV, yet what surprised us was the difference between the structures. Furthermore, Luteolin and HFI-142 almost identical predicted binding affinities and full fitness values. These findings provide new insight into the possible molecular underpinnings of *Ginkgo biloba*'s memory-enhancing effects.

*Keywords:* *Ginkgo biloba*, IRAP, nootropics, cognitive enhancement

## Introduction

*Ginkgo biloba* has many reported health benefits. It's often used to treat mental health conditions, Alzheimer's disease, and fatigue (Smith and Luo, 2004). It's been used in traditional Japanese medicine for about 1,000 years. It came on the Western culture scene a few centuries ago, but has enjoyed a surge of popularity over the last few decades. *Ginkgo biloba*, also known as the maidenhair tree, belongs in the family

Ginkgoaceae. The trees grow up to 35-50 meters or more. Their products are most popular during the fall season; it can be used to make tea or be added to various Japanese dishes.

Alzheimer's disease (AD) is known for reducing cognitive function and negatively impacting memory. There are still many mysteries of what triggers it, but now we are more aware that it starts long before any symptoms appear. There's a theory that it is caused by an abnormal build-up of proteins in the brain. Two of the proteins in this process are called amyloid beta and tau. Amyloid beta aggregate forms around brain cells and the Tau would tangle with the brain cell (Selkoe, 2001; Ballatore et al., 2007). After the proteins are in contact the brain cells become affected and decrease chemical messengers which are called neurotransmitters. These messengers are the key for signaling or sending messages between brain cells. According to the National Health Service (2019), throughout time, different areas of the brain shrink. Usually the first area that's exposed is the memories, which is the main symptom of Alzheimer's disease, but there are cases in which it affects the vision or language. Sometimes there are more unusual versions of Alzheimer's disease that affect different parts of the brain first.

Although the causes of Alzheimer's disease are not fully understood, there is evidence on what would increase or speed up the development of AD. Some of these causes are age, genetics, Down's syndrome, head injuries and cardiovascular disease. Age is one of the leading causes, for it doubles the chances of getting AD

every five years on average after you reach 65 (National Health Service, 2019).

The leaf extract is usually from leaves 15 cm wide and 8 cm long that remain on the branch 2 weeks after turning color. *Ginkgo biloba's* standard extract includes 24% flavone glycosides and 6% terpene lactones; this is known as EGb 761 (Smith and Luo, 2004). EGb 761 has several demonstrated neuroprotective effects, including the inhibition of amyloid beta aggregation. As such, EGb 761 shows a potential to become a preventative treatment for Alzheimer's disease (Smith and Luo, 2004). *Ginkgo biloba* extract has potential side effects, such as allergic reactions, bleeding disorders, diarrhea, dizziness, headaches, and constipation (Mayo Clinic, 2020). Most of these side effects are caused by overconsumption of the *Ginkgo biloba* leaf extract.

The *Ginkgo biloba* extract contains several primary terpenoids like bilobalide and ginkgolides A, B, and C. The primary flavonoids include quercetin, kaempferol, and isorhamnetin (Dziwenka and Coppock, 2016). Terpene lactones are one prominent metabolite found in the *Ginkgo biloba* extract. They are commonly used for an additional treatment for therapy in patients with ischemic cardiovascular and cerebrovascular diseases (Xin-wei et al., 2018). Furthermore, flavone glycosides are reported to have anti-inflammatory and antioxidant properties (Mahmoud et al., 2013).

There are a number of alternative medicinal products that reportedly improve cognitive function, known as nootropics, many of which include *Ginkgo biloba* extract. For example, Doctor's Best Extra Strength Ginkgo, 120 mg, is a best seller on iHerb. In the bottle, there is *Ginkgo biloba* leaf extract, which contains a minimum of 24% flavonol glycosides (28.8 mg) and 6% terpene lactones (7.2 mg) (iHerb). It states that the product increases memory and brain capacity and helps healthy mitochondrial and nerve cell function. However, the actual molecular mechanisms of this and similar *Ginkgo*

*biloba*-based products are unclear. Specifically, which molecules in the extract confer the memory enhancing effects- and how- is poorly understood.

IRAP stands for insulin regulated aminopeptidase. IRAP removes amino acids from extracellular signaling peptides. It also it helps with antigen presentation and cellular glucose uptake (Barlow and Thompson, 2020). IRAP inhibition is associated with improved cognitive function (Albiston et al., 2008). AngIV is a peptide and a well-known inhibitor of IRAP (Lew at al., 2003). IRAP has also been shown to be inhibited by non-peptide molecules, such as, 4H-benzopyrans, bosphinic pseudopeptides, 3,4-diaminobenzoic acid derivatives, aryl sulfonamides, and spiro-oxindole dihydroquinazolinones (Georgiadis et al., 2020).

*Ginkgo biloba* has shown many promising reasons to suggest that it has the ability to increase brain activity significantly. On the other hand, many students and researchers have indicated that it doesn't improve memory and brain activity. Here, we aim to determine whether molecules within the *Ginkgo biloba* extract can bind IRAP. Furthermore, we hope to understand whether *Ginkgo biloba* extract has the potential to serve as a cognitive enhancer. We use in silico methods to determine the binding affinity of two key molecules: luteolin and ginkgolide B. We hypothesize that luteolin and ginkgolide B will bind to IRAP and have similar binding affinities to known IRAP inhibitors.

## Methods

To test our hypothesis, we used computer simulation to model IRAP and potential inhibitors using a similar approach to Nakajima (2020). We used PDB structure 6YDX as our template for IRAP (Mpakali et al., 2020). From our literature, we found multiple ligands to choose from within the *G. biloba* extract. We chose luteolin and ginkgolide B (Li et al., 2018). For the positive control, the choice was AngIV (Barlow and Thompson, 2020). HFI-142 is a benzopyran that

represents our second positive control (Albiston et al., 2008).

During our research we've come across multiple software such as Chimera 1.14. After researching we designed the ligands in ChemSketch and exported each molecule as a .mol to Chimera 1.14. In Chimera, we selected Dock Prep and executed the following modifications to each protein: Delete solvent, Add Hydrogens, Mutate incomplete sidechains to ALA or GLY, Add charges using AMBER ff14S. Net charges for non-standard residues were assigned using the Gasteiger method (Junmei et al., 2006). Protein-ligand pairs were submitted to SWISS-DOCK.

Subsequently, we determined the proper docking by comparing the predicted clusters to the corresponding crystal structure for IRAP-AngIV. Next, we went to ViewDock and changed the Chain IDs by Edit text file to rewrite chain IDs for ligands. Finally, we used PRODIGY-LIGAND to calculate the change in Gibbs free energy,  $\Delta G$  (kcal/mol). The more negative the number, the more favorable the binding energy. Full fitness is calculated as the average of the top 30% predicted effective energies for a given cluster; effective energy is the sum of the total energy of the system (Grosdidier, et al., 2011). The best predictions for each ligand docking with IRAP were modelled and captured in Chimera.

## Results

The results of simulations in SWISS-DOCK and PRODIGY-LIG are shown in Table 1. Luteolin has the most negative full fitness value. However, AngIV has the lowest predicted  $\Delta G$  (-8.68 kcal/mol SWISS-DOCK; -9.6 kcal/mol PRODIGY-LIG). The difference of  $\Delta G$  between Ginkgolide B and AngIV is 1.3 kcal/mol; the difference of  $\Delta G$  between HFI-142 and Luteolin is much smaller (0.1 kcal/mol).

As shown in Figure 1, the structure of Luteolin (A) is similar to that of HFI-142(B). For instance, Luteolin and HFI-142 have three aromatic rings each, though HFI-142 contains an amine group.

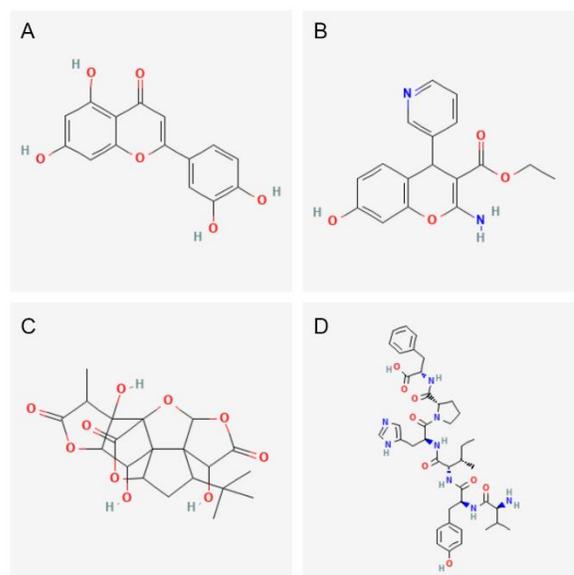


FIGURE 1: 2-dimensional chemical structures of Luteolin (A), HFI-142 (B), Ginkgolide B (C), and AngIV (D).

On the other hand, the structures of ginkgolide B (C) and AngIV (D) are quite different in both size as well as charge. As AngIV is a peptide, it is nitrogen-rich, whereas Ginkgolide B contains no nitrogen.

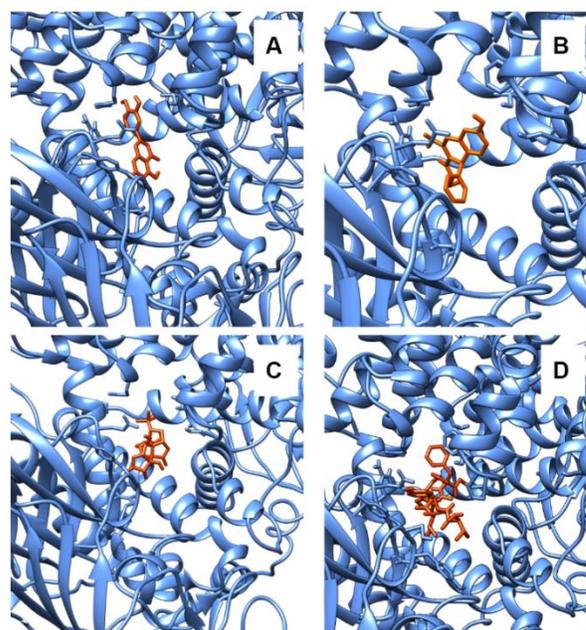


FIGURE 2: The predicted docking positions for each ligand with IRAP: luteolin (A), HFI-142 (B), ginkgolide B (C), and AngIV (D).

TABLE 1: Full fitness and $\Delta G$ calculations for each molecule.			
	Full fitness (kcal/mol)	$\Delta G$ (kcal/mol) (SWISS-DOCK)	$\Delta G$ (kcal/mol) (PRODIGY-LIG)
AngIV	-3873.60	-8.68	-9.6
Luteolin	-3988.18	-7.13	-7.6
Ginkgolide B	-3868.93	-8.44	-8.3
HFI-142	-3978.44	-7.10	-7.5

As shown in Figure 2, SWISS-DOCK correctly predicted the true binding site of AngIV (D). Furthermore, all of the best docking predictions were found to be in the same docking site as AngIV. All ligands interacted with GLU 426, GLN 922, SET 960, and THR 962. Luteolin (A) and HFI-142 (B) have nearly identical orientations within the docking site. HFI-142 was the only ligand to bind with ARG 439. As expected due its size, AngIV has more potential electrostatic interactions within the docking site than the smaller, non-peptide molecules tested; it also interacted with SER 207, GLN 293, ALA 961, and ASN 965.

## Discussion

The purpose of this study was to explore whether *Ginkgo biloba* extract can be used for memory enhancement. *Ginkgo biloba* extract contains a range of terpene lactones and flavone glycosides, including ginkgolide B and luteolin, respectively. Full fitness and delta G values tell us the affinity of our molecules to IRAP. When a molecule binds and inhibits IRAP, it has the potential to boost memory in the short- and long-term.

We found that luteolin had the most negative full fitness value of the four IRAP inhibitors tested, and that AngIV had the most negative  $\Delta G$ . Luteolin had similar predicted binding affinities as the known inhibitor, HFI-142. Interestingly, their chemical structures are also similar. This suggests that luteolin may be a promising memory-enhancing molecule.

AngIV was predicted to be the strongest inhibitor in both SWISS-DOCK and in PRODIGY-LIGAND. Ginkgolide B was found to have a similar full fitness and  $\Delta G$  values as AngIV in SWISS-DOCK, but a noticeably lower  $\Delta G$  in PRODIGY-LIG. That said, ginkgolide B had a more negative predicted binding affinity than both luteolin and HFI-142. It's possible that ginkgolide B is a better inhibitor than even HFI-142.

The conclusions that we can draw from this study are somewhat limited in that we only used silico methods. We did not test how the molecule is absorbed, metabolized, or delivered to IRAP *in vivo*. Future silico research should test additional molecules in *Ginkgo biloba* extract for their ability to inhibit IRAP, as well as test other relevant proteins related to cognitive function. After screening candidate molecules virtually, binding affinity assays could be done *in vitro*.

Ultimately, I would like to focus on how to utilize *Ginkgo biloba* extract safely while minimizing potential side effects. There are numerous nootropic products available that contain *G. biloba* extract, yet the underlying mechanism of actions are poorly understood. Nootropics have the potential to not only help alleviate the symptoms of cognitive decline associated with Alzheimer's Disease, but also provide a "brain boosting" effect for healthy adults and students alike. This work is a step forward towards understanding how natural nootropics, such as *G. biloba* extract, improve cognitive function and memory on a molecular level.

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# Climate Change and Allergic Respiratory Disease: an Overview of Effects on Children's Health

Leo Sun

Belmont High School, United States  
lsun23@belmontschools.net

## Abstract

Allergic respiratory disease and asthma, which each impact an estimated 20% of the population, are increasing in prevalence with the influence of climate change. Changing weather patterns resulting in stronger storms and worsening air pollution contribute to the threat that climate change poses to public respiratory health, increasing disease incidence and strengthening harmful exacerbations. Since children spend more time outdoors and have less resistance to air pollutants and aeroallergens, they are more susceptible to diseases like asthma and allergic rhinitis. Allergic respiratory disease has significant damaging effects on quality of life, causing physical health problems and hindering social and academic aspects of daily life. A systematic review was conducted to discuss the impacts of climate change on respiratory health, especially in children and adolescents. Action can and must be taken to prevent further health complications in the future—more widespread treatment methods, awareness of climate issues, and policy changes will go a long way.

*Keywords: climate change, allergic respiratory disease, children's health, asthma, allergic rhinitis*

## Introduction

The impact of climate change, commonly recognized as the 21st century's most significant health threat, is ever increasing in severity as human activities generate atmospheric

greenhouse gases. The widespread consequences of climate change include rising temperatures and increased frequency and intensity of extreme weather such as thunderstorms, floods, heatwaves, and hurricanes (D'Amato & Akdis 2020). Adverse environmental changes such as air pollution associated with ground-level ozone are also related to climate change (D'Amato et al. 2015), while particulate matter and other air pollution related to urbanization further contribute to respiratory allergic disease (D'Amato & Akdis 2020).

Asthma, the most common chronic disease in children and adolescents worldwide, develops from complex interactions between genetic factors, environmental exposures (Sheffield et al. 2011), and gene-environment interactions (Xu et al. 2018). In individuals affected by asthma or allergic rhinitis, the immune system mistakenly identifies environmental triggers such as allergens as dangerous to the body, releasing chemicals that can cause symptoms which include sneezing and congestion. An estimated 300 million individuals worldwide suffer from asthma and over 400 million from allergic rhinitis (Lake et al. 2017), costing tens of billions of dollars annually. Additionally, past literature has established that higher CO<sub>2</sub> levels due to climate change have a clear effect on bringing about earlier pollen seasons and higher pollen densities (Beggs 2015), enhancing photosynthesis, reproduction (D'Amato et al. 2015; Lake 2017), and plant

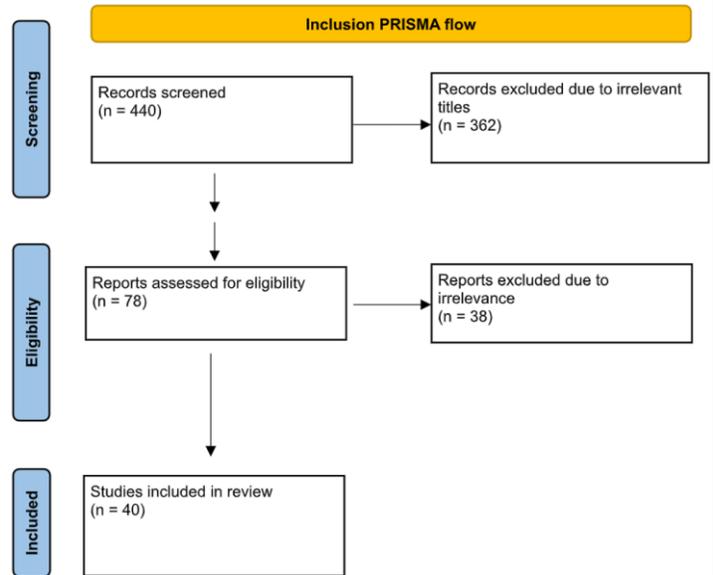
growth (Pawankar et al. 2020). Increased production of mold, pollen, and other aeroallergens will impact human health by increasing exposure to aeroallergens and worsening symptoms of allergic disease in affected individuals (Ziska et al. 2011). This will increase the risk of allergic respiratory diseases such as asthma and allergic rhinitis, the prevalence of which have been increasing in the past decades.

Moreover, thunderstorms strengthened by climate change have been shown to exacerbate asthma and allergic symptoms (D’Amato et al. 2015). Air pollution from traffic-related emissions and fossil fuels can further intensify the effects of aeroallergens on asthma exacerbation and allergic disease (Poole et al. 2019). Effects of climate change pose an increasing danger to respiratory health, especially in children, and more attention must be brought to this issue to improve future healthcare methods and reduce the burden of climate change on health. This paper systematically reviews existing papers and studies about the effects of climate change on allergic respiratory diseases and summarizes the implications those effects have on pediatric health. This review also aims to highlight research gaps and potential solutions for issues presented relating to children’s health in the future.

## Methods

Due to the relevance of climate change, there has been a rapid rise in the quantity of literature relating to this topic in the last several years. A systematic review was conducted using Pubmed, Google Scholar, and Proquest. Keywords used in the search include “climate change”, “pollen allergy”, “asthma”, “asthma in children”, and “childhood health”. 440 records were screened for titles and 78 were fully assessed for eligibility. Papers published after 2009 examining the effects of climate change on asthma or allergic respiratory disease or identifying impacts of asthma or allergic respiratory disease on children’s health and quality of life were included.

Records describing food allergy were excluded unless a significant mention of climate change or respiratory allergy was included. Articles focusing on air pollution were included if there was sufficient mention of climate change. 40 records that followed the inclusion criteria were included



in the final review.

FIGURE 1: PRISMA flow diagram of the systematic review conducted for this study

## Results

### *Climate change and allergic disease*

Various studies examined the effects of climate change on pollen prevalence using ragweed pollen. One such study used the recent ragweed invasion in Europe to demonstrate the effects of climate change on the development of the rather novel allergen to the region (Lake et al. 2017). They estimated that sensitization to ragweed will more than double from 33 million to 77 million by 2041-2060, with the greatest proportional increases occurring where ragweed sensitization is not yet common. This analysis shows that ragweed pollen may become a common health problem in the future without ample control of its spread in response to climate change (Lake et al. 2017). Another study on ragweed pollen in Europe determined an approximately fourfold

increase in pollen concentrations by 2050 (Hamaoui-Laguel et al. 2015). Stinson et al. (2016) grew ragweed plants at three latitudes in the northeastern United States, analyzing the effects of increased CO<sub>2</sub> levels on flowering periods. They found that elevated CO<sub>2</sub> resulted in flowering an average of 2-3 days earlier. Furthermore, plants from higher latitudes flowered for an average of 5 days longer than those from lower latitudes. These results provide evidence for a correlation between higher CO<sub>2</sub> levels and flower production, duration, and potential pollen output (Cecchi 2018), with a possibility of more drastic effects in latitudes further north. Above 44° North, the ragweed pollen season may have been prolonged by as much as 13-27 days since 1995 (Ziska et al 2011). Pollen-counting stations in the United States have also shown an earlier start in the pollen season in the most recent decade (Zhang et al. 2015). Additionally, a 27-year-long study using extensive pollen monitoring data in Italy found a progressive increase in pollen season length and sensitization to pollen throughout the period (Ariano et al. 2010), correlating with the increase in temperature due to climate change.

Climate change will also increase the frequency and severity of thunderstorms, impacting respiratory health. A number of studies assessed the effects of thunderstorms on asthma and respiratory allergy. It has been shown that the first phase (20-30 minutes) of a thunderstorm can cause increases in the number of allergens in the air (D'Amato et. al 2016) as wet conditions rupture pollen grains, possibly resulting in severe asthma attacks or even death in susceptible individuals (Pawankar et al. 2020; D'Amato et al. 2020). One particular study showed that the occurrence of asthma epidemics is linked to thunderstorms and is limited to late spring and summer when there are high levels of airborne pollen grains (D'Amato et al. 2014). Additionally, 2016, the warmest year on record before 2020, witnessed the most severe thunderstorm asthma event ever recorded (Katelaris et al 2018), with an

estimated 3365 more respiratory-related hospital emergencies than expected. A questionnaire study of this event showed that 57% of patients did not have prior asthma diagnoses and that rhinitis, found in 88% of subjects, was highly prevalent, with 71% reporting moderate to severe symptoms (Pawankar et al. 2020). Thunderstorms pose a real danger to susceptible individuals and staying indoors when they occur should be recognized as an important precaution to avoid health complications.

Furthermore, air pollution and climate change are closely associated. For example, burning fossil fuels generates significant amounts of greenhouse gas, including CO<sub>2</sub>, which contributes to climate change (Eguiluz-Gracia et al. 2020). Acute ground-level ozone exposure resulting from climate change is linked to childhood respiratory illness and increased emergency department visits related to asthma (Sheffield et al. 2011), and may even cause new cases of asthma in the long term. Studies have demonstrated that ozone increases asthma morbidity by enhancing airway inflammation and hyper-responsiveness (Guarnieri & Balmes 2014; D'Amato et al. 2014; Sheffield et al. 2011). In addition, as many individuals spend much of their time inside in westernized countries, high exposure to indoor allergens such as dust mites, tobacco smoke, and other pollutants can be expected (D'Amato et al. 2016), harming respiratory health. Outdoor air pollution from sources such as traffic has similar effects, but can also enhance the allergenicity of certain plants and contribute to global warming (Eguiluz-Gracia et al. 2020). Further, air pollution can harm children's lung development, adding to the adverse effects of respiratory disease. Epidemiological studies have demonstrated that urbanization and high levels of vehicle emissions correlate with a greater frequency of respiratory allergy in urban populations, especially in children living near traffic (D'Amato et al. 2015; D'Amato et al. 2016). The risk of epidemic rise in allergic diseases is more severe in the Asia-Pacific region

due to its rising urbanization in recent decades (Pawankar et al. 2020). These developing consequences of climate change necessitate consideration of potential health impacts on children in particular.

#### *Allergic disease and children's health*

The increasing prevalence of respiratory disease due to climate change disproportionately affects children's health as a result of their cognitive and physical immaturity (Anderko et al. 2020). The World Health Organization states that 88% of the global burden of disease attributed to climate change occurs in children less than five years old, particularly those in low-income countries. Children may also be at a higher risk of developing asthma or allergic disease by spending more time outdoors and being exposed to outdoor pollutants and allergens (Sly & Holt 2018; D'Amato et al. 2014).

The prevalence of allergic disease in children has various studied causes. For instance, exposure to harmful environmental factors may be able to affect the health of a child even in the fetal stage of development (Anderko et al. 2020; Gern 2010); there is accumulating evidence establishing a link between prenatal and early-life stress and the development of asthma in children (Rosa et al. 2018; Lam et al. 2014). Exposure to mold, moisture, and maternal smoking in the first year of life (Lam et al. 2014) have also been shown to increase the risk of asthma and rhinitis (Cecchi et al. 2018). Furthermore, an analysis of the 2016–2017 US National Survey of Children's Health found that adverse childhood experiences, such as household economic hardship, an incarcerated parent or guardian, and household and neighborhood violence were all associated with higher odds of reported moderate or severe asthma (Ross et al. 2021).

A study of common diseases in children took place in South Africa, where decadal warming rates of 0.1°C to 0.3 °C were observed. The most prevalent diseases found in the study group were diarrhea (42.4%), respiratory infection (31.3%),

asthma (6.6%), and malaria (6.5%) (Thompson et al. 2012). These diseases correlate with climatic variations due to climate change and are the leading causes of death among children. Male children were more susceptible to the prevalent diseases that were observed, possibly a result of their greater interaction with the outdoor environment. Similarly, older children are more susceptible to asthma and rhinitis (Yamamoto-Hanada et al. 2020), while younger children experience a greater incidence of respiratory infection—likely due to lower immunity against airborne allergens (Thompson et al. 2012). There is also evidence of an increasing incidence of pollen-food allergy syndrome, particularly in adolescents, which may be related to the rising prevalence of allergic rhinitis and pollen allergy (Kiguchi et al. 2021; Cudowska et al. 2021).

Several studies demonstrated the implications of respiratory diseases such as allergic rhinitis and asthma on quality of life for children and adolescents. In the United States, the prevalence of allergic rhinitis in individuals aged 14 to 17 was estimated to be 24.8%, and this number will likely continue increasing. Furthermore, adolescents with allergic rhinitis or asthma were found to have a lower quality of life, affecting daily function, sleep, school productivity, and academic performance (Blaiss et al. 2018; Proctor et al. 2020; Kiotseridis et al. 2013); higher levels of anxiety, depression, and hostility, along with shorter durations of nighttime sleep were also noted (Blaiss et al. 2018). Interestingly, the negative impact on quality of life was more severe in adolescents than younger children and adults. This difference is likely due to common lifestyles focused on school, in which these symptoms more strongly interfere with patients' ability to complete daily activities, achieve goals, and maintain family relationships (Blaiss et al. 2018). In young children, wheeze is the most common symptom of asthma, and it has been shown to disrupt sleep one or more times a week until age 3 (Yamamoto-Hanada et al. 2020). At ages 2 and 3, rhinitis caused disturbances to the daily

activities of about 5% of children. Similarly, a study of grass pollen allergy symptoms in children found a strong association between pollen count, symptom severity, and health-related quality of life during the pollen season (Kiotseridis et al. 2013).

## Discussion

These results show that climate change is worsening respiratory allergy and disease through increased air pollution, lengthened pollen season, greater production of aeroallergens, and changing weather patterns. Consequently, severe impacts on children's respiratory health must be considered to prevent future health implications as climate change progresses and the population continues to grow. Children have lower immunity to airborne pathogens and spend more time outside; therefore, their age group is more vulnerable and requires particular attention. In addition, pollen allergy and asthma have far-reaching effects: financially, with medication expenses, and socially, by interfering with daily activities such as work and school. Improved management of allergic respiratory diseases could help reduce disease burden on daily functioning, quality of life, sleep, and academic performance, especially in children and adolescents (Blaiss et al. 2018).

Addressing and finding solutions to specific health issues will be essential. For cases related to severe asthma, which includes about 5% of populations with asthma, close therapeutic relationships between medical practitioners and patients can effectively manage the disease (Ahmed & Turner 2019). Adaptation measures to climate change that work to reduce ozone levels, such as cleaner-burning fuels and vehicle emission limits, may be able to synergize with efforts to manage asthma (Sheffield et al. 2011). In regards to pollen-food allergy syndrome, a significant danger to adolescents that is often linked to rhinitis, poor knowledge of the subject in patients can be mitigated by early intervention and more thorough education (Kiguchi et al. 2021). Of course, capturing epidemiological

signatures will continue to be essential to document burdens of disease and to design health care services, including prevention measures, clinical interventions, and policies (Yamamoto-Hanada et al. 2020).

Action can be taken to address issues raised by climate change. Effective training and preparation of future healthcare providers will be essential. Moreover, proper education of individuals with respiratory allergy and asthma may help patients avoid unnecessary risks such as staying outdoors during thunderstorms. Additionally, it will be important to coordinate efforts between legislatures, administrators, and the public to take steps to combat air pollution and slow global warming (Pawankar et al. 2020). Parents can ensure that their children are not exposed to a contaminated environment and stay safe with advice from healthcare professionals. Further, increased awareness of climate change may allow for stronger environmental conservation programs, enforcement of safety precautions, and more readily available treatment.

A very promising method of allergy treatment is allergen-specific immunotherapy, the only clinically effective treatment capable of modifying IgE-mediated allergic diseases (Arasi et al. 2018). It is helpful as a therapeutic option to intervene during the early phases of respiratory allergic diseases in childhood, when disease progression can be more easily influenced. Growing evidence supports allergy immunotherapy as a way to treat allergy; one study showed a 50% improvement in quality of life after 3 years of therapy (Proctor et al. 2020). This strategy may even work to prevent the development of new allergic diseases in patients. However, the methodologies of its administration are not standardized, and more study must be done surrounding its long-term benefits.

Some limitations to this study include a lack of access to some sources of relevant data. For example, various topics explored in the review such as thunderstorm asthma would have benefited from more detailed source material; a

greater database pool could resolve this issue. Additionally, although significant progress has been made in this field in recent years, there are still many areas where further research is necessary. For one, the majority of pollen studies were completed in the northern hemisphere and often focused on ragweed and tree pollen. As notable trends may vary in different regions, research in the southern hemisphere is warranted (Beggs 2015). Furthermore, knowledge about treatments for allergic disease is lacking and should be a focus of future research to combat climate change.

In conclusion, climate change is heightening the danger of allergic respiratory diseases, with children at the highest risk of allergen exposure. Moderation of the main risk factors for respiratory disease such as air pollution and better management of asthma and rhinitis are necessary and will have significant long-term health benefits.

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## Retinal Detachment Is in The Eye of the Beholder

Tara Suri

Stuyvesant High School, United States

tarasuri20@gmail.com

“Just hear those sleigh bells jingling, ring ting tingling too.” Music crackled out of our family’s radio. My mother’s humming filled the air, while we decorated our Christmas tree.

Excitement permeated the room because we would be leaving for vacation in a few weeks. As we decorated our Christmas tree, my brothers and I talked about what we wanted for Christmas. With gleeful grins, we imagined our presents tied up with thick red bows and colorful wrapping paper under our tree. When we asked our mother what she wanted, she responded, “A new pair of glasses would be nice, but I need my eye prescription before we leave for our vacation in India.” As she strung red-colored beads around our tree, she excitedly told us that designer glasses were very cheap in India and how she was going to buy a few pairs. My brother and I thought nothing of it. We continued to hang ornaments on the tree and talked about our upcoming trip. This would be our first time going to see the Taj Mahal, one of the Modern Seven Wonders of the World. We were also excited to visit our paternal grandparents’ home because they had just renovated it and were planning to throw a big party for family and friends.

A week later, as I walked into the hallway, I brushed the snow off my boots onto the carpet and my mother took off her coat and hung it on the coat rack. I approached the receptionist and gave her our names, and my mother signed the attendance sheet. The tune of Jingle Bells music could be heard playing faintly in the background. We sat down on the gray-colored armchairs and

waited for the doctor. I began to browse and casually flip through the random magazines strewn on the coffee table. I looked to see what my mother was reading and noticed that her Glamour magazine was resting on top of her baby bump. Suddenly, we were called into the exam room. We walked into exam room no. 2 and continued to wait for the doctor. My mom raised up her magazine to show me an ad for a black pair of designer sunglasses that she hoped she would find in India. The ophthalmologist arrived and he started the eye exam. The exam seemed routine until the doctor put a lens over my mother’s eye and flashed a big light. As soon as he looked through the ophthalmoscope, everything changed. The ophthalmoscope is a special instrument with a special magnifying lens that provides a detailed view of the whole eye, allowing the doctor to see any retinal holes, tears or detachments.”

What the ophthalmologist saw was a retinal tear in her left eye. A retinal tear occurs when the vitreous (a colorless, gel-like substance) contracts and tugs on the retina. The retina is a thin layer of light-sensitive tissue that lines the back of the eye. The retina is vital to sight because when light enters through the eye, it must pass through the retina, so that the electric impulses can be sent to the brain allowing us to see.

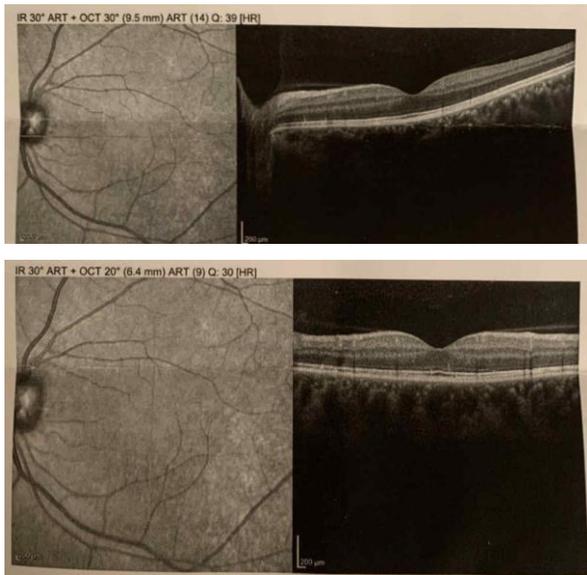


Figure 1: These images show the layers of the retina. The photos were taken with an OCT (optical coherence tomography) imaging machine, it is a non-invasive imaging test that uses light waves to take cross-section pictures of the retina. These images were taken in December right before my mother had laser surgery done. The line it shows the beginning of a retinal tear.

The doctor further questioned my mother about whether she had recently experienced any of the following warning signs that almost always appeared before retinal detachment occurred or has advanced, such as appearance of floaters — tiny specks that seem to drift through your field of vision, flashes of light in one or both eyes (photopsia), gradually reduced peripheral vision, or a curtain-like shadow over your field of vision.

My mother responded that she did not seem to notice the symptoms to be occurring. However, she indicated that she did notice a few floaters on some occasions which she thought was normal.

Next, the doctor proceeded to inform her that retinal tears, if left untreated, would lead to retinal detachment, which would lead to blindness. Retinal detachment is caused when fluid passes through the tear that is formed from a retinal tear and causes the retina to be ripped away from the supporting tissue. If this happens, your vision is

affected because the retina is unable to function properly. In the areas where the retina detaches, blood supply is lost, which leads to blindness.

After his explanation of retinal tears, the ophthalmologist sent my mother to a special machine to perform a non-invasive imaging test called Optical Coherence Tomography (OCT). OCT uses light waves to take cross-section pictures of your retina. The OCT allows the ophthalmologist to see each of the retina's distinctive layers and their thickness. These thickness measurements are used to help with diagnosis and treatment.

I saw my mother sit in front of the OCT machine and rest her head on a support to keep it from moving. She looked into two viewfinders. Then the machine equipment scanned her eyes without touching it. Scanning took about 5 to 10 minutes. She said she saw bright orange lights inside the viewfinders, similar to a morning sunrise.

Over the next two days, my mother saw several ophthalmologists, who all recommended surgery called the scleral buckle. A scleral buckle is when a piece of plastic or other hard material band is placed on the sclera. Unfortunately, the doctors were not willing to operate on my mother because she was at the end of the second trimester of her pregnancy. As a result, my mother had to make several visits to doctors to explore alternatives to surgery. Additionally, the winter holidays were in two weeks and many doctors were leaving for vacation. All of them agreed that treatment was necessary and had to be performed immediately. Yet, all the doctors were hesitant about administering surgery on a six-month pregnant lady because there were potential health risks to the baby.

One day after one of my mother's appointments, she came home with an eye patch. I ran over to my mother, asking her what was on her eye. She explained that she had a procedure performed called photocoagulation. The procedure uses a laser where the laser beam travels through the pupil and burns the tissue around the retinal tear, acting as a binder to the underlying tissue. My

mom explained that during her procedure, she sat in front of the laser machine and the ophthalmologist sat opposite of her on the other side of the machine. The laser procedure was performed on an outpatient basis. She said that as a result of the procedure, she had to avoid activities that might shake or rattle her eyes — such as running — for the next couple of weeks. As a child, all I understood at the time was that my mother might go blind, and she needed treatment right away. That was terrifying for me, and the thought of becoming blind was even tougher on her. During the few days after the procedure, she looked like a mysterious movie star, always wearing sunglasses indoors. I thought she looked awesome back then. Now I realize that she had to wear them because of how sensitive her eye was from the treatment.

During the next few days that my mother sought her second or third opinion from the various ophthalmologists, details concerning the trip were becoming unclear. Late at night, I would hear hushed whispers coming from my living room as my parents discussed if we would be traveling to India. Back and forth, my parents would talk about the flight tickets that were already purchased and non-refundable, the effects of airplane cabin pressure, the possibility that something else could happen to my mother's eye during the trip. My brothers and I were disappointed as we thought about all the fun we would miss if my parents cancelled the vacation. It is only now that I truly understand that my mother was concerned about the effect of air pressure on her recently treated eye.

Turning onto the runway, our plane started to prepare for takeoff to India. I glanced over at my mother. She was always a nervous flyer, but this time she looked different. She closed her eyes gently as the plane gradually rose up into the air. She took deep breaths. She clung to the sides of her seat. She mumbled to herself "It will be alright." The thirteen-hour flight had just begun. During the flight, she didn't experience anything

strange, and we were all thrilled when we finally landed in New Delhi.

The doctor told us that if she had waited any longer, she could have gone blind. My mother never expected this to happen to her. She serendipitously went into her eye appointment. She told me later that the only other symptom that she experienced that was out of the ordinary was when she would stare closely at the mirror, her left eye would swell up with tears. The sudden appearance of many tiny specks, random shadows, and flashes of light in her vision did not used to occur.

Some of the factors that potentially increased my mother's risk of retinal detachment is her family history of retinal detachment and myopia. Eyes were never a strong suit in my family. My mother's side of the family has a history of eye problems. I remember asking my mother why this happened to her. My mother would tell me about her grandma. "She would have a lot of water coming out of her eyes and she had difficulty seeing." I didn't understand how this could just happen to someone. I asked my mother why she didn't go to the ophthalmologist more often if she knew of family members with the same problem. My mother thought that eye problems only happened to the elderly, not pregnant women. Also, my grandma was never diagnosed because she was a housewife's farmer in China with limited access to healthcare. Limited eyesight causes mobility issues. My great grandmother had difficulty traveling by herself anywhere outside her home. My grandmother recalled that she and her siblings had to assist my great grandmother with many of the daily chores around the house. I listened to these stories with fascination.

Studies have shown there may be a correlation between retinal detachments in Southeastern Asians compared to European White race persons. This is because Southeastern Asians tend to have a higher risk of myopia, in addition to a longer axial length.

In Singapore, 1993 to 1996, 1126 retinal detachment operations were performed. The

average annual occurrence of retinal detachment operations was 10.5 per 100,000 people. The annual incidence was highest for Chinese: 11.6 per 100,000, and the lowest was for Indians: 3.9 per 100,00. The age relative risk of retinal detachment operation for Chinese compared with Indians was 3.0. My mother's family is from southeastern Asia, specifically China. According to the evidence recorded from the 1126 test subjects, the risk for people of Chinese descent are about 10 percent more likely to be diagnosed with retinal detachment. This study shows how retinal detachment is more prevalent in certain races and might be a reason why my mother suffered from a retinal tear.

Three months later, the time came for my mother to give birth. It was a difficult experience where my mother was concerned about her eye as well. My mother was very nervous about the whole ordeal. She worried she would strain her eye while giving birth. Doctors warned her about the possible dangers of the effects of giving birth. Sometimes during the second stage of labor, the face is under a lot of strain and blood vessels in your eyes can burst. Because her laser surgery was supposed to be a temporary fix, my mother wasn't sure if it would hold through the delivery, or she would need to have eye surgery performed after delivering the baby. When she was in labor, she tried not to push from her face, and used her stomach muscles.

It has been six years since my mothers' laser, and she still goes for her bi-annual checkups at her ophthalmologist. (See Figure 2 below for the condition of the eye in 2019)

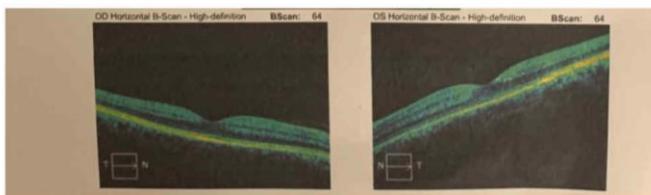


Figure 2

Note: These images were taken after my mother's laser surgery. The photos show that the tear was sealed by the laser and the eyeball is intact in 2019.

But I know that psychologically, she will never be the same. Although my mother's physical condition is holding up, she often checks her peripheral vision to try to determine if she is losing her field of vision. In the morning, she often complains that she is seeking a lot of shadows. Sometimes at night, she claims she is seeing flashes and has to lie down for a while to rest her eyes. She thinks that it is possible that something could happen to her other good eye. I sometimes worry about my own eyes. Wondering if I have inherited genes that will lead to eye problems in the future.

When I researched my mother's condition, I realized that the anxiety she experienced was common. Patients undergoing surgery commonly experience psychological effects such as anxiety or depression. Preoperative anxiety is usually influenced by the patient's concern about his or her general health, uncertainty regarding the future, post-operative pain, and loss of independence. Preoperative anxiety exists where patients experience disquietude before surgery that continues to grow after surgery. Researchers have correlated the degree of preoperative psychological stress and recovery and emphasize the importance of emotional factors in treatment. Studies done in Saudi Arabia stated that psychological disturbance reported only by 17.5 percent of the studied patients. "Preoperatively 71 percent of them showed mild to moderate anxiety. After the procedure, 80 percent of anxious patients maintained or experienced a decreased level of anxiety. In addition to anxiety, 20 percent of anxious patients developed postoperative mild depression. 14 percent of the psychologically disturbed patients had moderate depression before surgery which became milder

after it. Another 14 percent showed severe anxiety and moderate depression only postoperatively. Severe visual impairment was reported by 86 percent of psychological disturbed patients.” These percentages show that there are many psychological effects that occur to patients during the pre-operative stage and post-operative stage of retinal detachment that warrant medical treatment as well.

The engine hummed as we drove along the highway. Lights flashed as cars zoomed past us. My mother drove slowly. “Why are we driving so slow?” I asked, peering through the dark. No one was near us. “It's hard to see.” My mother replied. I wondered what she was talking about. It was dark, but definitely not pitch black. “The lights are too bright nowadays; it's hard to drive, ” she added. I took a look at the other side of the highway at the cars traveling in the other direction with their headlights on. The lights didn't look strange to me. My mother explained that “The red lights did not used to look like this. I used to be able to drive at higher speeds during the night.” I can never truly understand what my mother experiences on a daily basis. My mother told me once that “It's almost like someone is taking a picture of you with the high flash on, except when you look around there's no one there.” Even though the laser procedure has kept the retina attached, I know that her vision is not the same. Occasionally, I can see the worry in my mother's eyes, and she will suddenly close her eyes because she sees a flash of light or a shadow. There is tension in her voice, as she asks if a bug flew past because she is unsure if she saw a bug or spots floating around. Sometimes, when we are outside, she sees shadows move across her line of sight when there are none. My mother becomes weary from her vision problems. Although my mother can see, her worry never ceases. A person's life really is in the eye of the beholder.

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# Evaluation of Kyogen Costume Storage Environment and Calculation of Proper Temperature Setting for Energy Conservation Effect Using Fungal Index

Edison Suzuki

The American School In Japan, Japan  
edomitsu.suzuki@gmail.com

## Abstract

The American School in Japan has had a Kyogen club since 1978. Kyogen is a Japanese deadpan comedy with a 650-year history, from the Muromachi period. When performing Kyogen, student actors wear special Kyogen costumes called “sho-zoku.” The school stores these costumes in boxes made of paulownia wood in the storage room. However, no studies have been done before on the environmental conditions inside the paulownia box and the storage room to determine if they are suitable for maintaining expensive “sho-zoku.” Therefore, in this study, data loggers that can measure temperature, humidity and fungal index were installed on the shelf and inside a paulownia box for 10 months to measure these environmental conditions. As the result of analysis of measured data and calculation, two main results were obtained. The first result was that when the “sho-zoku” were stored in a paulownia box in the storage room, the fungal index value was kept low without undergoing sudden changes in the ambient relative humidity. The second result was that in the summer, if the air conditioning temperature in the storage room is set to 30.4°C, the relative humidity will decrease to 67.5% or less. As a result, the fungal index value will stay below the threshold value of 1, meaning that there would likely be very little mold in the environment. Also, the power consumption of the air conditioner will decrease by 54%.

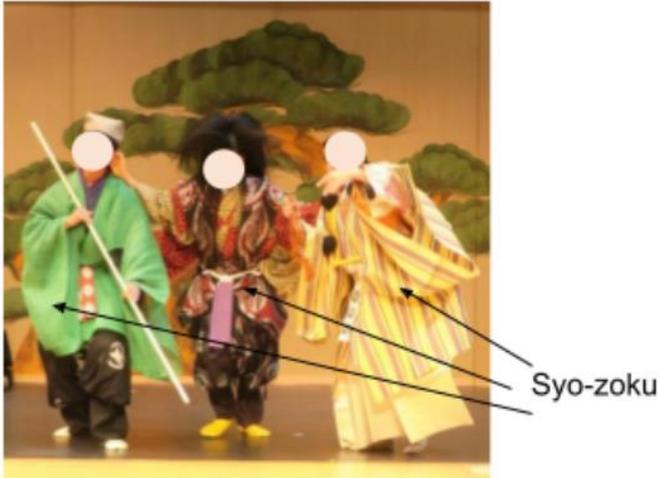
*Keywords: fungal index, paulownia box, relative humidity, psychometrics, energy conservation effect*

## Introduction

The American School in Japan (ASIJ) has had a Kyogen club since 1978 (The American School in Japan, 2018). Kyogen is a Japanese deadpan comedy with a 650-year history, from the Muromachi period (Salz, 2016). Kyogen masters from the renowned Yamamoto family have been coming to the ASIJ school campus for over 40 years to teach the students to perform. When performing Kyogen, actors wear special traditional costumes called “sho-zoku (Figure 1).” The school stores these costumes in boxes made of paulownia wood, which is said to have moisture regulating effects, and have been used to store books and kimonos for centuries in Japan (Aoki, 1999, Seya & Tazawa, 2016, Angelov, 2019). However, there has been no example of verifying whether the environmental conditions inside the storage room and paulownia boxes are really suitable for maintaining expensive “sho-zoku.” Therefore, in this study, devices that can measure temperature, humidity and fungal index were installed on the shelf and inside a paulownia box for 10 months to measure these environmental conditions. Then, the obtained data was used to consider the appropriateness of the current “sho-zoku” storage method. In addition, the obtained

actual measurement data was used to derive results of calculating the appropriate temperature and humidity conditions for suppressing mold growth using a psychrometric chart (ASHRAE, 1992, Callahan, 2019) and results of trial calculation of the amount of power consumption reduction.

FIGURE 1: A scene from a Kyogen performance (February, 2019, at the American School in Japan)



## Materials and Methods

### *Storage room where measurements were taken*

This study was conducted in a storage room in the school that stores costumes for musical drama performances and Kyogen “sho-zoku.”

### *Measurement period*

The measurement period was from June 11, 2020 to April 24, 2021. However, from February 4 to 13, 2021, the paulownia box containing one temperature/humidity logger was taken out of the storage room and placed in the backstage area of the school theater, so the temperature and humidity data during that period measured the backstage environment. This data was excluded from statistical data analysis.

### *Measurement of temperature, humidity and fungal index*

The wireless fungal logger LR8520 (Figure 2, HIOKI E.E. CORPORATION, Nagano, Japan) was

used to measure the temperature, relative humidity, and fungal index of the environment in the storage room. One logger was installed at the center of the shelf in the storage room. A second logger was installed in a paulownia box containing the “sho-zoku” (Figure 3). The logger measurement interval was set to 10 minutes. From June 11 to December 13, 2020, a third logger was installed in a cardboard box without a lid containing props and also stored on the shelf. The fungal index is an indicator of mold growth in an environment developed by Dr. Keiko Abe. The fungal index was measured and calculated by the fungal sensor where standard fungal spores are enclosed in the paper cell (Abe, 2010, 2012a, 2012b, 2016, Abe & Murata, 2014).

FIGURE 2: A logger placed on a shelf

FIGURE 3: A logger placed inside a paulownia box



The diagram of the relationships among the fungal index, temperature and relative humidity indicates

that the fungal index determines spore germination more depending on the relative humidity than on the temperature (Abe, 2012a, 2012b, Kurashima, 2016). The measured fungal index values for various rooms in buildings in Japan have been published previously (Abe, 2012a, 2012b, 2016, Abe & Murata, 2014). A fungal index of around 50 is equivalent to that inside bathrooms in residences in Japan, and a fungal index of 100 or higher is equivalent to that inside air conditioners in residences in Japan (Abe, 2012a, 2012b, 2016, Abe & Murata, 2014, Kurashima, 2016).

#### *Paulownia box*

The paulownia box in which the “sho-zoku” were stored are of the following dimensions: length 95 cm, width 42 cm, height 19 cm (Figure 4).



FIGURE 4: A paulownia box storing “sho-zoku”

#### *Statistical processing*

The data were found to be nonparametric, and were statistically compared between two groups by the Mann-Whitney U test (Schober et al., 2020) using the IBM Statistical Package for Social Sciences (SPSS) version 27.0 (IBM Corp., Armonk, NY).

*Calculation using actual measurement data to find the temperature at which the fungal index does not exceed the threshold of detecting mold*

A free Excel™ software add-in “Psychrocals” released by the University of Vermont (University of Vermont, 2021), which is based on the calculation method according to ASHRAE (American Society of Heating, Refrigerating and Air-Conditioning Engineers) handbook, was

downloaded and used in Excel™. Using this add-in, a calculation was performed to find the temperature at which the fungal index remains under the threshold even in the environment where the relative humidity in the measured data is the highest.

## Results

### *Measurements of temperature, humidity and fungal index*

The temperature data measured on the shelf and inside the paulownia box for the entire measurement period is shown in Figure 5. The relative humidity data measured on the shelf and inside the paulownia box is shown in Figure 7. The fungal index data measured on the shelf and inside the paulownia box is shown in Figure 9.

The temperature, relative humidity, and fungal index data measured on the shelf and inside the paulownia box for every month during the measurement period are shown in Figures 6, 8 and 10, respectively.

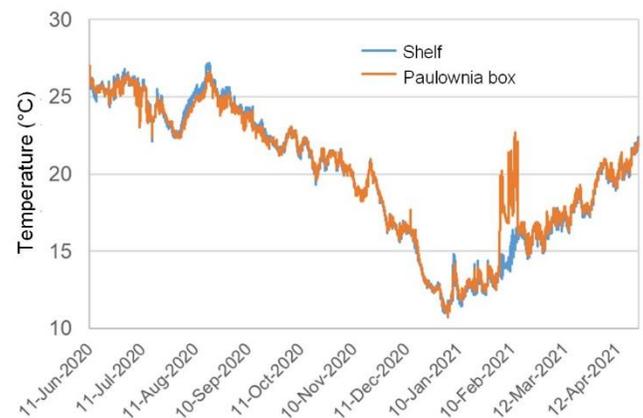


FIGURE 5: Temperature data of the measurement period

The maximum temperature was 27.2 °C on the shelf and 27.0 °C inside the paulownia box in August 2020. Throughout the measurement period other than February 4-13, 2021, no major statistical differences could be observed between measurements on the shelf and inside the paulownia box (Figure 5).

Every month during the measurement period, there was no significant difference in temperature between measurements on the shelf and inside the paulownia box in June, July, November, and December 2020. In August and September 2020, the temperature on the shelf was significantly higher than that inside the paulownia box (Figure 6,  $p < 0.01$ ), and in October 2020, January, February, March and April 2021, the temperature inside the paulownia box was significantly higher than on the shelf (Figure 6,  $p < 0.01$ ).

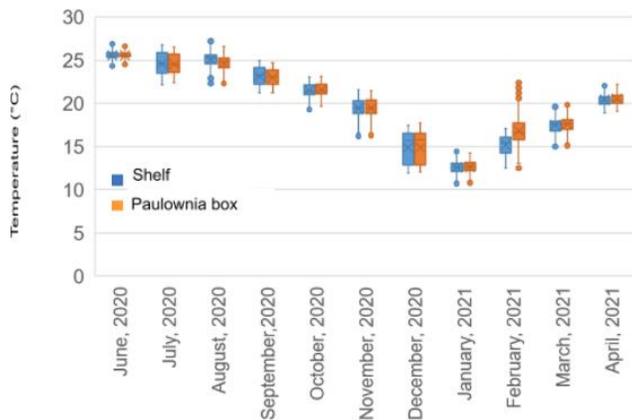


FIGURE 6: Temperature data by month

Over the entire measurement period, the maximum relative humidity on the shelf was 92.0% on July 28, 2020, and the maximum relative humidity inside the paulownia box was 85.0% on August 18, 2020.

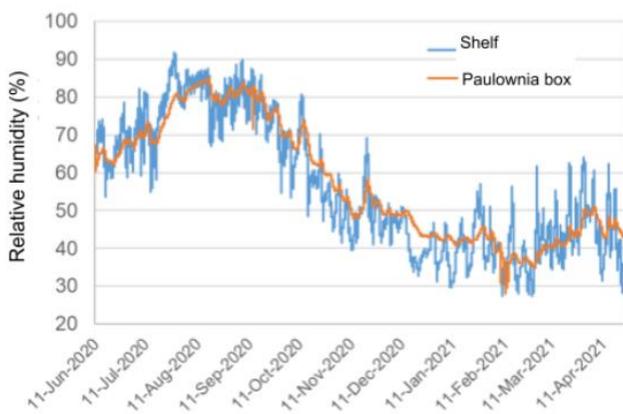


FIGURE 7: Humidity data of the measurement period

Throughout the measurement period other than February 4-13, 2021, the relative humidity (RH)

inside the paulownia box (median 52.3% RH) was slightly higher than that on the shelf (median 52.1% RH) (Figure 7,  $p < 0.01$ ).

Every month during the measurement period, RH was significantly higher on the shelf than in the paulownia box in June and July 2020 (Figure 8,  $p < 0.01$ ), similar in both locations in August 2020, and significantly higher inside the paulownia box from September 2020 to February 2021, and April 2021 (Figure 8,  $p < 0.01$ ).

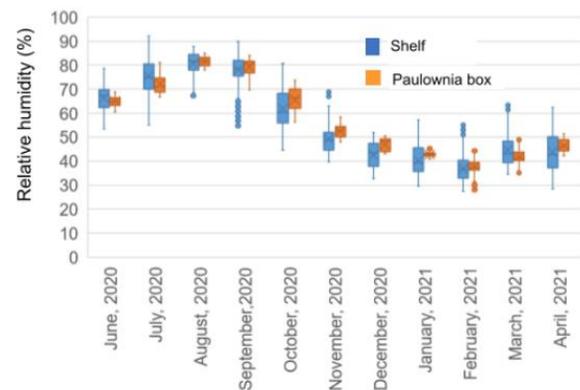
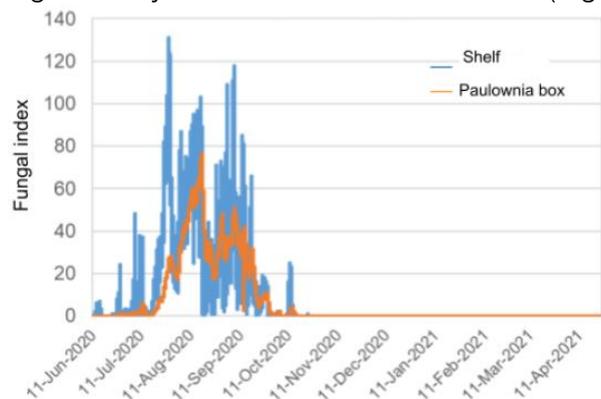


FIGURE 8: Humidity data by month

Throughout the entire measurement period, the maximum fungal index value on the shelf than in the paulownia box was 131 on July 28, 2020 and 77 inside the paulownia box on August 18, 2020. Throughout the entire measurement period, the fungal index inside the paulownia box was significantly lower than that on the shelf (Figure 9,



p < 0.01).  
FIGURE 9: Fungal index data of the measurement period

Every month during the measurement period, the fungal index value was significantly higher on the shelf than in the paulownia box in June, July and October 2020 (Figure 10,  $p < 0.01$ ), was similar in both locations in August 2020, and in September 2020 the value was significantly higher inside the paulownia box (Figure 10,  $p < 0.01$ ). The fungal index value remained below the mold detection threshold from November 2020 to April 2021. The measurements indicated that the fungal index was not detected when RH was below 67.5%, and the fungal index was 1 when RH was 67.6%.

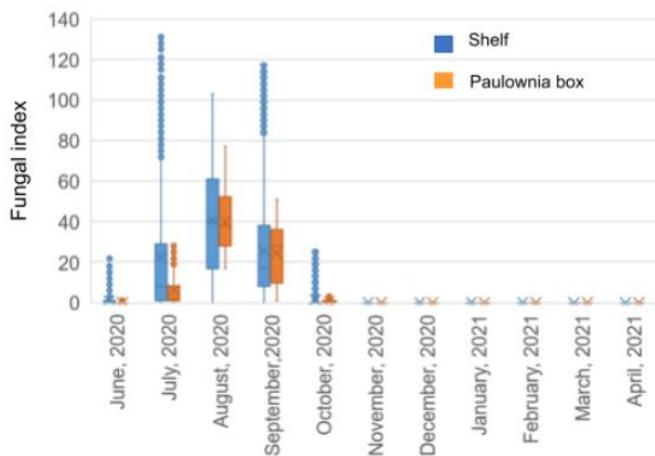


FIGURE 10: Fungal index data by month

A histogram of the temperature data of June, July, August, and September 2020 on the shelf is shown in Figure 11. It was found that the temperature with the most measurement points was 25°C, and for measurement points that exceeded 26°C, the number of measurement points decreased to about 2/5 that of 25°C (Figure 11). From this, it can be concluded that the air conditioning temperature setting in the storage room during this period was mostly likely 25°C.

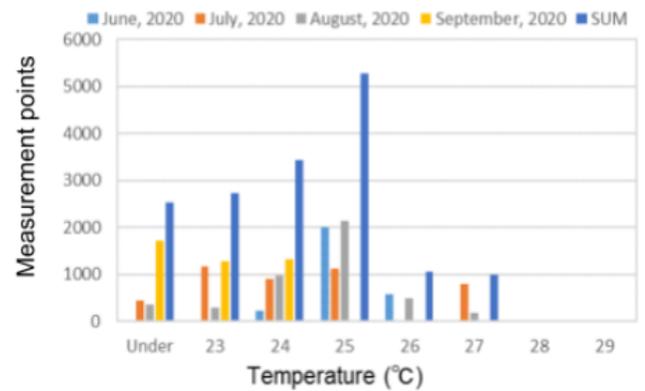


FIGURE 11: Histogram of temperature on the shelf (June, July, August, September 2020)

*Calculation of the temperature at which the fungal index is sure not to exceed the threshold of mold detection, using temperature and humidity measurement data and psychrometric charts*

From data of actual measurements of temperature, humidity and fungal index in this study, it was determined that the fungal index did not exceed the threshold of mold detection when RH was 67.5% or lower. Psychrometric charts (ASHRAE, 1992, Callahan, 2019) indicate that for a closed space in which the total moisture in the room remains constant (such as the room for storing the “sho-zoku”), an increase in temperature will result in a decrease in RH. For the dates and times of actual measurements showing RH values that were too high, it is worth noting by how many degrees the temperature should have been increased to bring RH down to 67.5%. Psychrometric calculations were performed to derive the temperature at which the fungal index is sure not to exceed the threshold of mold detection, for all cases of measurements of the designated period of time.

Calculations were performed to obtain a psychrometric chart for RH values 92.0% and 67.5% by calculation from the measured data from June 1 to September 30, 2020, the period with the highest RH of all measurement periods in the storage room. The temperature and humidity data during the same duration obtained by

installing the 3rd logger in the cardboard box with the top of the shelf unclosed on the shelf was also added for this calculation.

The temperature data measured in this study is the dry-bulb temperatures (Tdb), and the humidity data is RH. All plots of RH versus Tdb (from all data of the 3 sensors of June 1 to Sept 30, 2020, where RH > 67.5%) are shown in Figure 12, indicating that the maximum RH value is 92.0%.

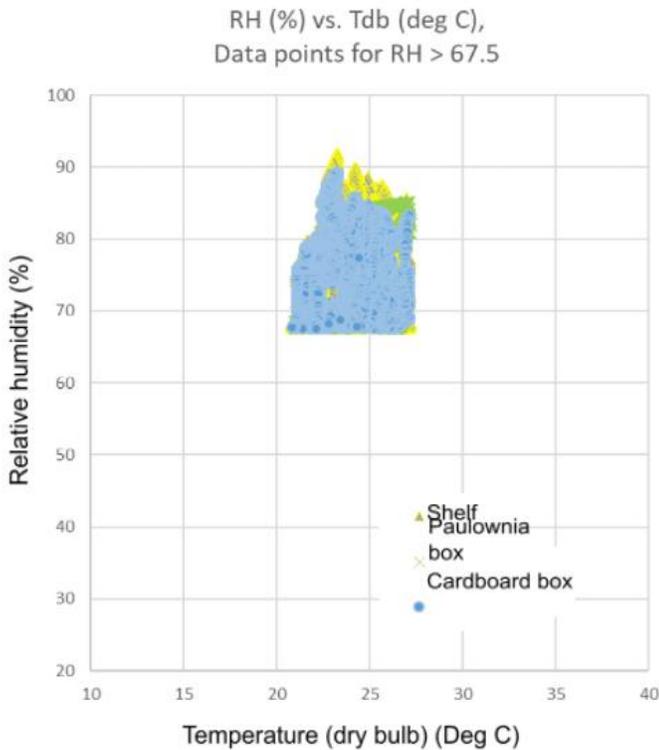


FIGURE 12: The relationship between relative humidity (RH, %) and dry-bulb temperature (Tdb), data points for relative humidity >67.5%.

As the next step, Twb (wet-bulb temperature) was calculated from Tdb, RH, and the atmospheric pressure (which was assumed to be 1 atm = 14.6959 PSIA (absolute pounds per square inch)) according to psychrometric functions (University of Vermont, 2021). Then the Humidity ratio (Hrat) was calculated from Tdb, Twb, and the atmospheric pressure. The plot of the calculated Hrat versus Tdb were shown in Figure 13, showing that the maximum Hrat value is 0.01926.

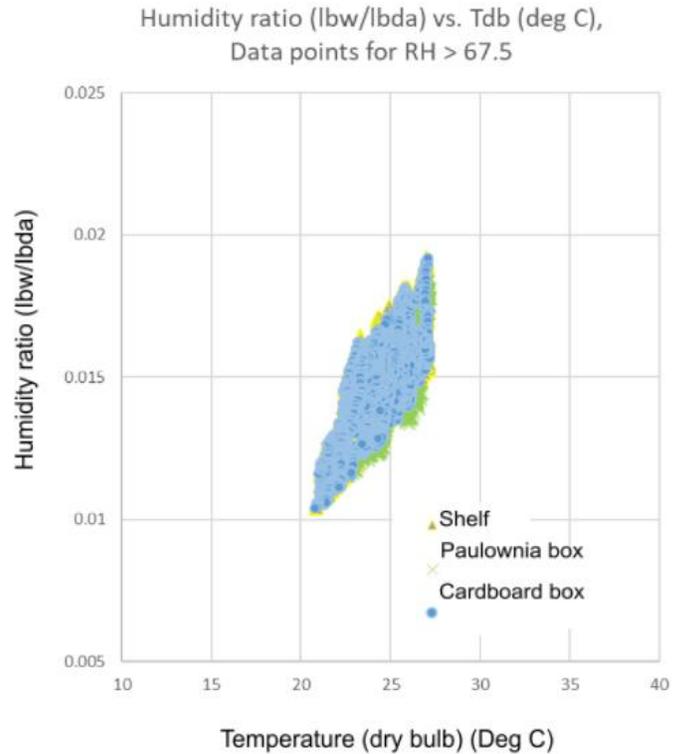


FIGURE 13: The relationship between humidity ratio (lbw/lbda) and dry-bulb temperature (Tdb), data points for relative humidity >67.5%.

Then, the plot of the calculated Hrat versus Tdb for the two cases of constant RH, of 67.5% and 92.0% were expressed in Figure 14. The case of 67.5% RH was plotted because that is the maximum RH value for which the fungal index will not exceed the threshold for detecting mold. The case of 92.0% RH was plotted because that is the maximum RH value for all data of the 3 sensors of June 1 to Sept 30, 2020. Then, in Figure 14, Tdb where Hrat = 0.01926 was found to correspond to 25.8°C when RH = 92.0%. Tdb where Hrat = 0.01926 was found to correspond to 31.2°C when RH = 67.5%. The difference in temperature is 31.2 - 25.8 = 5.4°C. So, by raising the temperature setting of the air conditioner in the storage room by 5.4°C, the resulting RH will be 67.5% or lower, which would minimize the risk of mold growth.

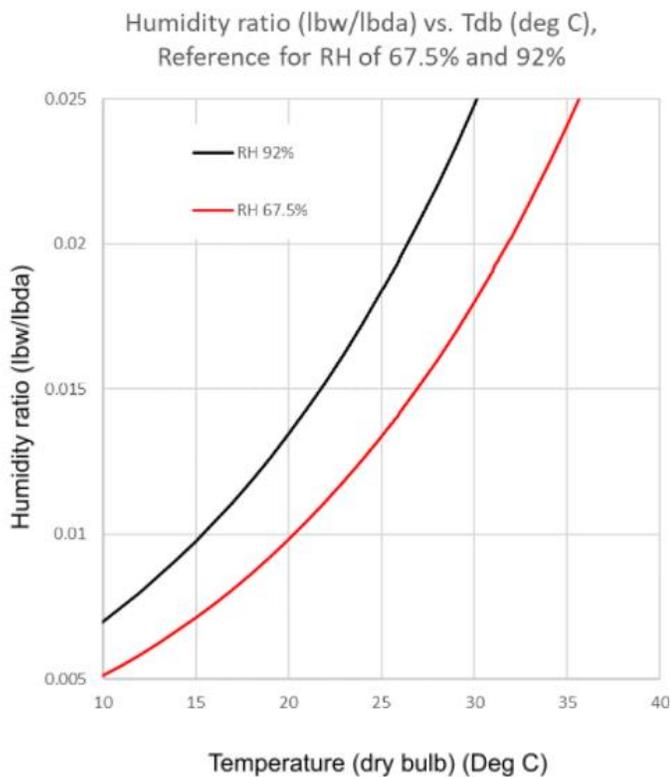


FIGURE 14: The relationship between humidity ratio (lbw/lbda) and dry-bulb temperature (Tdb), reference for relative humidity 67.5% and 92.0%.

### Discussion

*Environmental conditions for measurement in the storage room on the shelf and in the paulownia box*

The fungal index inside the paulownia box was found to be significantly lower than that on the shelf, with the exception of the index found to be high only in September 2020. In September 2020, the humidity change in the storage room was large, and the fungal index on the shelf also changed significantly in response to the change in humidity. However, in the paulownia box, the variation of the monthly RH data was small. From these results, the fungal index was considered to be stable in the paulownia box because it is not easily affected by sudden changes in RH in the storage room, and RH in the box can be maintained with even greater stability.

Not only does the paulownia box prevent dust in the storage room and airborne microorganisms that are attached to dust particles from adhering to the “sho-zoku,” storing the “sho-zoku” in the paulownia box helps maintain the fungal index at a low level and avoid mold growth, which are vital to avoiding the deterioration of the “sho-zoku”.

Paulownia lumber has long been considered to be excellent for storing and preserving classical books and ancient documents in Japan, and paulownia boxes have long been used as storage containers for various cultural materials. The reason why paulownia is used is that it does not produce tar, is resistant to insect damage, and is also resistant to sudden changes in the humidity of the outside the paulownia box (Aoki, 1999). The results of this study confirmed the effect of the paulownia material in mitigating the effects of the humidity change of the outside air on the humidity inside the paulownia box. On the other hand, even if the fungal index can be kept low in the paulownia box, the inside of the storage room and the paulownia box still need to be cleaned regularly to remove dust and mold spores attached to the dust. Considering the growth time of mold spores, the optimum cleaning time is after October when mold spores grow (Lee et al., 2006).

*Storage room environment indicated by fungal index values*

The highest fungal index value of 131 obtained on July 28, 2020 on the shelf was equivalent to the environment inside a bathroom in a residential environment or an air conditioner during cooling, and was equivalent to the environment in which it took less than 12 hours for the outbreak of mold and took 2 months until the start of fungal contamination (Abe, 2012a, 2012b, 2016, Abe & Murata, 2014, Kurashima, 2016). The index value of 77 obtained in the paulownia box on August 18, 2020 was also found to be equivalent to an environment in which it took less than 1 day for the outbreak of mold and took about 4 months

until start of mold contamination (Abe, 2012a, 2012b, 2016, Abe & Murata, 2014, Kurashima, 2016). It is possible to keep the fungal index value lower by storing the “sho-zoku” in the paulownia box rather than directly placing the costume on the shelf without any box. However, it was still necessary to reduce RH in the storage room so that the median fungal index value in the paulownia box in July, August and September 2020 was 20 or less, which is about the index value found in the average home in Japan.

#### *Reducing relative humidity in the storage room using results of calculation*

Since the fungal index depends on RH in the environment, it is effective to lower RH in order to lower the fungal index value in the storage room. For that purpose, options were considered to (1) directly dehumidify the storage room, or (2) raise the control temperature in the storage room to lower RH. Regarding (1), since the storage room air conditioning system does not have a dehumidification mode, it is difficult to reduce RH directly by mechanical dehumidification. Also, if a separate dehumidifier is installed in the storage room, the accumulated water cannot be disposed during the long summer months when the school is closed. Therefore, it is difficult to perform mechanical dehumidification directly. On the other hand, regarding (2), it is possible to raise the control temperature in the storage room as follows.

Within the measurement period, June to September 2020 is the time when the air conditioning setting of the school is in the cooling mode, and even though there are no people and no activity in this storage room, the air conditioning was controlled in the cooling mode all the time. From Figure 11, it was inferred that the upper limit of the control temperature in the storage room was 25°C in the summer. It was estimated that if the air conditioning temperature was set to 30.4°C, which results from the addition of 5.4°C as obtained from the calculations, RH in

the storage room would be 67.5% or less, and the fungal index would not exceed the threshold of detecting mold. In the summer, people do not enter the storage room for any activities, so it is not necessary to set the temperature inside the storage room in consideration of thermal comfort for human beings. Therefore, it is considered feasible to set the storage room temperature to 30.4°C to lower RH.

#### *Energy expected to be conserved by raising the control temperature setting*

Furthermore, the reduction of power consumption, that is, the reduction of consumption cost, can be realized by raising the air conditioner control temperature by several degrees. For air conditioning management in offices, there is an idea such as “night setback” that reduces the cost of air conditioning power consumption (Izawa & Fripp, 2018, Pacific Northwest National Laboratory, 2012). During the time when people are in the office, the temperature is set to within the range that people feel comfortable, and during the night when there are no people in the office, this “night setback” is implemented such that the temperature range is set to levels that exceed human comfort (raised in the summer, lowered in the winter).

The storage room where the “sho-zoku” is stored is not a room occupied by people for any extended period of time. Therefore, it is not necessary to set the temperature for time division such as the “night setback,” so the storage room environment can be easily adjusted to reduce air-conditioning costs.

According to the Ministry of the Environment in Japan guidelines (Ministry of the Environment in Japan, 2021), U.S. Department of Energy (U. S. Department of Energy, 2021), and North Carolina State government (North Carolina State government, 2010) for controlling greenhouse gas emissions and the optimization of air-conditioning control temperature and humidity,

raising the air-conditioning setting by 1°C will reduce power consumption by about 10%. In the estimation in this study, the control temperature setting was increased by 5.4°C, suggesting that the air conditioning power consumption in the storage room in the summer could be reduced to about 54%, that is, about half of the current settings.

## Conclusions

It was found that when the “sho-zoku” Kyogen costumes in the storage room are stored in a paulownia box, which can absorb moisture very well, the fungal index value was kept low without undergoing sudden changes in RH.

In the summer, if the air conditioning control temperature in the storage room is set to 30.4°C, RH will be suppressed to 67.5% or less, and as a result, the fungal index will not exceed the threshold of mold detection, and an energy conservation effect of about 54% can be expected.

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# Japanese student movements of the 1960s and 2010s: comparing Zenkyoto and SEALDs

Emily Tanaka

Tabor Academy, Japan

emilytanaka1009@gmail.com

## Abstract

Zenkyoto in the 1960s and SEALDs in 2015 are among the largest student-led movements that have occurred in Japan. This research paper seeks to explore the connections between both eras and to identify effective tactics for youth social and political engagement in Japan's unique post-war climate by analyzing and comparing its strategies and its circumstances. The seemingly contradictory desire of today's Japanese youth to engage in politics without activism reflects the enduring fear of radicalization and violent conflicts with police. SEALDs attempted to address these fears by pioneering digital spaces for members to connect and by making fashionable branding core to their growth. Japanese youth social movements are ultimately driven less by identity-based challenges, but rather circumstantial issues borne from the desire for democratization following World War II. As Japan pursues globalization, it will be key for youth to step out of their comfort zone for more exposure to the world.

*Keywords: Student social movement, youth political engagement, SEALDs, Zenkyoto, youth*

## Introduction

During the COVID-19 pandemic, the United States saw an increase in social and political activism. In some ways, the pandemic brought to light systematic inequalities that were no longer tolerable for many Americans. While America was the epicenter of many movements, such as the

resurgence of the Black Lives Matter (BLM) movement, it spread to many other countries. In Tokyo, a BLM protest was held, yet it lacked the focus and energy of its American counterparts. The lack of connection between politics and the daily lives of Japanese youth was apparent not only at that protest but also throughout the greater part of the last fifty years. In the Nippon Foundation's Awareness Survey, only 20% of Japanese youth believe they can change their country or society, whereas almost half of the youth answered as 'interested and want to engage in politics and social movements' (Tominaga, 2021). This contrast shows an interesting perception of youth's perspective of such movements. After the wave of student movements of the 1960s, activism became less visible and it became difficult for youth to consider going against the people in power in Japanese society. Nonetheless, the acknowledgment of political and social issues, and addressing them for improvement are crucial to achieving a world with more inclusivity, equality, and equity. I seek to find out the possibility of historical reasons by comparing two past student movements in Japan and to look for effective tactics for youth social and political movements by finding the answer to those two questions: How has history affected student movements in Japan? What makes a successful youth movement in Japan? I argue that contemporary youth movements in Japan have several parallels with movements from the 20th century; however, the perceived radicalization of

the earlier movements has led to discouragement and cynicism today.

Student-led social and political movements in Japan have evolved over time, often reflecting parallel movements occurring beyond its borders. The All Japan Federation of College Student Governments, *Zengakuren*, was at the forefront of student-led activism. Its ideologies reflected the dominant ideas of communism and nationalism in the early 1900s in Japan. The ideology of nationalism and communism leading to World War II raised awareness in youth. For instance, the *Study Group on Military Matters* and *National Student Union Against Military Training* were both founded in 1923 to promote two opposite ideas concerning military issues, one for pro-militarization and one for anti-militarization. Even high school students were inspired to be engaged in the student movements such as *Koto-gakko-Remmei*. Furthermore, *Gakusei Shakai Kagaku Rengo-kai* was a student federation of social science that reorganized in 1924 as the Student Group of Communist Youth (Shimbori, 1963).

The anarchy of the political and ideological orders due to the destruction of the economy led to the decreasing number of student activists after World War II. Most of the post-war activists were elites who focused on democratic reform; the majority of people were only thinking of surviving the next day.

“Thus, in this period, when the only power elite was the occupying forces which could not be criticized or attacked, and when the people consumed their whole energy in maintaining a mere existence there could not be a student movement of a political kind.” (Shimbori, 1963)

The ideology and tactics of the movement seemed to become more radical as time passed in most cases. The moderate claim for democracy and liberalism developed into a demand for socialism and communism in extreme. Those student movements in the past also show that the

ideology with a more diverse attitude holds a greater number of participants in their movements.

By looking at the timeline in Figure 1, the student movement is likely to appear first in times of social emancipation such as the 1923 Tokyo earthquake, World War II, Vietnam War, and 2011 earthquake (Shimbori, 1963).

### **Zenkyoto and Yasudakoudoujiken**

Similar to pre-war movements, national political matters stimulated the students' movements in post-war; however, post-war movements generally focused on liberal democracy and globalism. By cooperating with non-student organizations, they were involved more as citizens rather than students. At the boundary of , many visible student movements came to an end that might have led to the declining number in visible youth engagement.

After World War II in Japan, many students were asking for democratic reform at their schools and a greater say in school administration. It started as in-school issues with the students and authorities; however, students started to feel threats to their welfare because the government organized policies such as drastically increased fees, decentralization of national universities, and the “Red Purge” of 1949 (Shimbori, 1963). The All-Campus Joint Struggle, *Zenkyoto* (全学共闘会議), was a student union formed to organize the university protests that are promoting democracy and their academic freedom in the 1960s. This union eventually became an organization with 168 national, 31 municipal, and 61 private universities (Shimbori, 1963). While some *Zenkyoto* were founded by students with democratic ideology who challenged Japanese politics, some other movements focused on non-political and local issues as well. Much of *Zenkyoto's* activity in the late 1960s turned into clashes between students and police due to its radicalization.

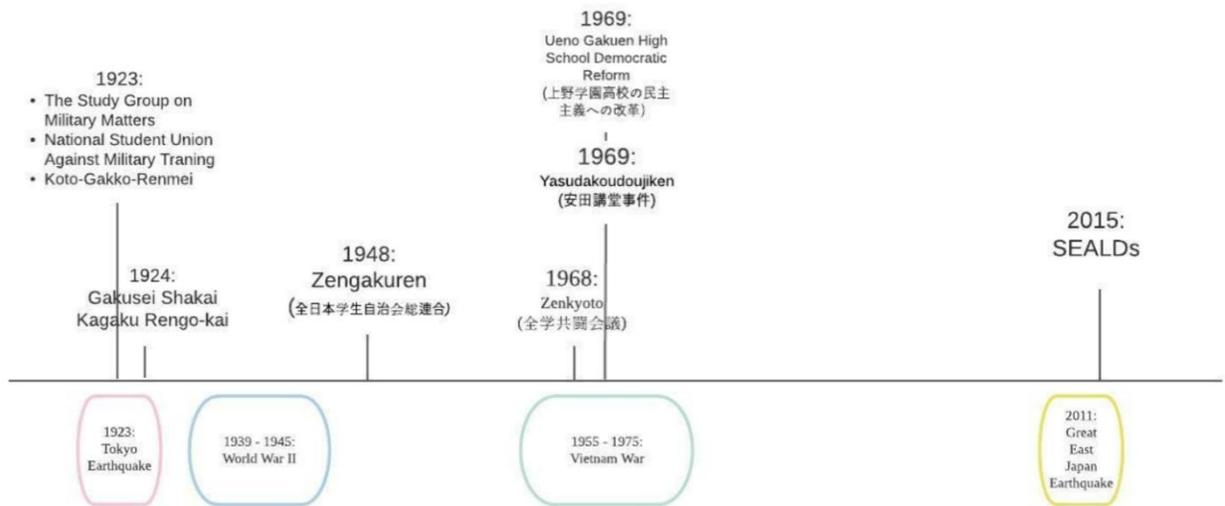


FIGURE 1: Timeline of select student movements in Japan.

TABLE 1: Answer to the question, “What do you think may be the cause of the increasingly violent and radical student activities?” Percentages represent participants that responded “Yes.” (Adapted from Fuse, 1969)

	Harsh political and economic realities in Japan	Lack of students' sense of responsibility
Students	86%	50%
Professors	82%	46%
Public school teachers	71%	57%
Parents	63%	51%

The survey, Table 1, was taken in 1967 and before the *Yasudakoudoujiken* that represents an interesting insight on students' and teachers' perspectives on the radicalization of student activism. *Asamasansoujiken* is one of the cue incidents that demonstrate the radicalism in Japanese student movements; the rising tension led to irrationalism and violence where it lost its focal point of their activism. While the majority of

youth and adults agreed on blaming the deconstructed economy after the war and on alternation in Japanese politics from communism to democracy, almost half of the youth and adults also agreed on criticizing the “students' lack of responsibility”. This could indicate that even with the understanding of difficult circumstances in politics and the economy in Japan, some believed that students should have been more responsible with their actions.

The University of Tokyo group, called *Todai Zenkyoto* (東大全共闘), started in January of 1968. Led by *Todai Zenkyoto*, *Yasudakoudoujiken* (安田講堂事件) initially started as a protest against the intern system for medical students in the University of Tokyo (Todai). Their intern system, following six years of medical education, was brutal. Graduates were forced to work for low pay as a doctor which was only 1000 dollars per month (大人の教養TV, 2020). The medical students asked the authorities to abolish this intern system and apologize; nonetheless, the university disregarded their demand which eventually led to the occupation at the main auditorium in *Todai* from their outrage and frustration of feeling unheard and being portrayed as the ‘bad guys’. The students started to self-govern in the auditorium called *Yasuda Koudou* by teaching classes among themselves and having meetings.

The authorities asked them to go back to their normal life which none of the students listened to. Instead of proposing a compromise, they sent the riot police. Thus, 8,500 police officers were around the building ready to break in anytime (9章 東大紛争). The students used Molotov cocktails and throwing stones to fight back the police force and argued that using police force disrupted the constitution of independent schools where they supposedly have freedom of autonomy. Throughout their occupation time, the students asked for explanations and proposed multiple terms; however, the authorities ignored them and kept on going with the police force. Eventually, students had to give up on the occupation from their mental and physical exhaustion after a year and with the cancelation of the entrance exam. Moreover, they could not succeed in making the change which resulted in the extinction of student movements from their realization of helplessness in making changes and not being heard.

#### **Local student movements: a first-hand perspective**

I was fortunate to interview Yoko Sugimura who witnessed one of the largest waves of student movements in Japan. She was a freshman high school student in 1969 when her school, Ueno Gakuen, underwent a student-led reform. Although the reform could not last due to students' dispiritedness to continue the unique style of the school system as years went by, her school also went through democratic reform by creating a new educational system and valuing 'self-learning' with their supportive teachers. Furthermore, Yoko explained that the difference between the modern social movements in America and those past student movements in Japan is that Japanese activism were not about systematic oppression regarding people's identity such as race or gender. Now looking back to those movements, she feels that it was a privilege and a nice gesture of liberalism (Y. Sugimura, personal communication, July 22, 2021).

#### **SEALDs and Article Nine**

Multiple factors contributed to the declining political engagement following *Yasudakoudoujiken*. The clashes between students, authorities, and policies in the 1960s left an unwelcoming impression on student activists (Chun, 2015). The urgency in lack of interest and engagement in politics and social activism among youth in Japan stood out when the reconstruction of Article 9 in the Japanese Constitution occurred. As the outgrowth of the Students Against Secret Protection Law (SASPL), the Student Emergency Action for Liberal Democracy (SEALDs) was founded in 2015 in Tokyo against it. SEALDs influenced many students to be more politically engaging throughout Japan including the lead for a protest against the policies of the prior Prime Minister Shinzo Abe with over 100,000 people (Chun, 2015).

Seeking to distinguish themselves from the violent image of radical political engagement in the past, SEALDs started to encourage Japanese youth to be engaged in politics and social matters. Rather than just leading with politics, they incorporated music, art, and popular culture into the activism to express inclusivity and to have 'fun' without offending others (Aonuma, 2016). By raising awareness and reminding them of the relevance of politics and their daily lives, they focused on challenging Japanese young people to explore more often in those topics. Some of their strategies took advantage of a hybrid of cyberspace and urban space to execute their brand of activism by using the networked cyberspace and physical urban spaces for self-directed education to protect Japan's liberal democratic values and promote constitutionalism. By utilizing cyberspace well, they expanded their capability throughout their activism in building on local knowledge, involving relevant stakeholders, and demonstrating connective leadership (Ute & Malcolm, etc, 2016). Those capabilities played a big role to motivate the youth around them to be more politically engaged. They were successful in creating inclusive project governance during their

activity which assisted a wider variety of people to join their organizational practices. One of the SEALDs members once described their movement in comparison to the past student movements in the 1960s and 1970s, he said:

“...we think that social movements before us seemed unapproachable, scary, and uncool for young people. I don't mean to totally disregard all the old social movements that have happened before us, and I know that there have been people who did something meaningful and fought for their causes. However, they were a bit hard for us to identify with, so we are trying to get rid of that scary image. I think it's an important factor to be fashionable and to use music in order to attract our generation so that we raise our voice.” (O'Day, 2015)

The purpose of their movements was to expand the horizon of their view on political and social matters with inclusivity by embracing new tactics in cyberspace and advocating the sense of normality in the political youth involvement. They brought their attention to the violent and 'uncool' image of the students' movements due to the rising intensity and irrationalism in the 1960s. Hence, their main focus was a modification in the image of social and political engagement to attract youth indifferent to the activism.

While SEALDs came to an end after about a year, it became a turning point for Japanese youth to realize the relevance of politics in their daily lives which was an advancement. Moreover, they made a significant impact on refreshing the image of violent and radical student movements to a peaceful and inclusive organization to achieve a better future.

Overall, they succeeded in breaking the norms and challenging the apathetic image of Japanese youth politics and speaking up to protect Japan's liberal democratic values. Their demonstration of non-violent tactics presented a rational image in the engagement of youth in politics to the public

by projecting the pertinence of their freedom and life choices in their future (Falch and Hammond, 2020). By questioning ethical development in recent years and asking how to improve their ways of living, they encouraged Japanese youth to raise awareness in the lack of exploration of social and political matters. Moreover, their ability to mobilize a large number of youths by taking advantage of cyberspace led them to become one of the first large organizations in the 21st century in Japan.

### **Similarities and differences of Zenkyoto and SEALDs**

*Zenkyoto* and SEALDs challenged Japanese youth to spread the sense of normalization in political and social engagement by applying different tactics according to their eras. They both valued autonomy and self-governance. The act of maintaining self-governance is important for the success of sustainable social movements (Ute & Malcolm, etc, 2016). For instance, due to the outside force of police coming in during their movements, *Todai-Zenkyoto* had an even stronger aspiration for self-governing which led to the meetings, lectures, etc at *Yasudakoudo's* occupation. This goes similarly for SEALDs as well where they had a certain structure within their community for self-governance. They created their way to sustain their movement with their 'do it yourself' spirit (Falch and Hammond, 2020). Moreover, the high school Yoko went to, Ueno Gakuen High school, demonstrated self-governance through their democratic reform initiated by students. Despite the time being uncommon of having the support from adults, their teachers decided to support students' idea of reform within themselves. They acted as leaders to encourage students to have more autonomy and independent studies for them to have more freedom in their academic careers.

To achieve the goal, both activisms were maximizing the utilization of space according to their eras. For instance, it brought much attention to *Zenkyoto's* movements when the occupation of

*Yasudakoudoujiken* happened in 1969 at the University of Tokyo. Forty-six years later, SEALDs was able to utilize not just the physical space, but cyberspace as well by using social media or creating a website for easy access for more participants. Social media were used to appraise the news of politics and social issues and spread the idea of normality of getting in touch with politics for younger people. Their website made their mission, statement, and activism clear and informed their point of view on politics as well, such as regarding the issue of Article 9 (Falch and Hammond, 2020).

One of the interesting things that both Zenkyoto and SEALDs have mentioned in some articles was that they enjoyed being with their friends and hanging out together. One of the former Zenkyoto members once said they were bringing alcohol and snacks inside of a blockade to drink together to just have fun and that they were not totally isolating themselves from the outside world. Seemingly, many of them were just looking for these gatherings with their peers (Miyazaki, 2001). Similar to Zenkyoto, one of the SEALDs' members also once mentioned having fun with their peers:

“It was fun and, particularly with the music and everything else, it also felt cool,” Suzuki says. “When I first started going I was particularly impressed by the speeches. I felt like I was learning things that filled a gap in my education. We’d dress for the protests wearing the same as if we were going into Shibuya with friends. It’s just the same as going out to have fun — it really feels as if it’s something connected to our everyday life.”(Sunda, 2015)

Though they were passionate about bringing changes to their community with seriousness, they also seemed to enjoy their time together to achieve the goal they created. Enjoying each others' company and having fun helped establish a sense of camaraderie.

## **Identity and its role in social movements**

When Yoko mentioned at the end of the interview, she explained the idea of privilege comes into play when she thinks about the difference in student movements in Japan and the United States. Although Zenkyoto movements were focused on school democratic reform, it can also be said as improving their school life; wherein contrast, many political movements in the United States ties into identity discrimination and equal human rights such as Black Lives Matter. Moreover, the initial intention of forming SEALDs was focused on political matters (issue of Article 9), yet is not directly tied to identity discrimination. Not just with the fact that most of the leaders of those movements were elites; even so, due to those privileged circumstances, some may argue those student movements were “rich kids playing at politics” (O’Day, 2015). Being able to speak up for their improvement in their school life can be seen as a gesture of liberalism in Japan. Their goals and circumstances can impact their passion and momentum in those movements.

One of the SEALDs members mentioned their graduation and passing the torch for the interview of *The Japan Times* in 2015 as part of the SEALDs' ending (Shibata, 2015). Though they explained that SEALDs was an ‘emergency’ organization for protesting against the abolishment of Article 9, it can also be described as a privileged gesture of being able to decide the time to put a pause to their movement. As opposed to those Japanese student movements, the ethical identity-based movements cannot and should not have a moment for a pause until there is justice for those who have been discriminated against due to their identities.

## **Conclusion**

Perhaps the difference in focus led to the differentiation of students' social and political engagement. Compared to the United States, Japan is a relatively ethnically homogenous country; as such, most people rarely encounter

identity-based discrimination on daily basis, which can make it difficult to raise awareness. Nonetheless, as globalization expands in Japan, ignorance can cause identity discrimination. Accordingly, it will be important to have more exposure to a variety of social and political news and issues to be aware of in those subjects.

“I often remind young people that our country is not democratic, our country is authoritarian,” Gonoï says. “So we have to utilize this ‘boomerang effect’ because the Japanese media including the likes of NHK and the Asahi Shimbun, shirk under the influence of the government, which is why they don’t report on these protests directly. After an article (on youth activism) is published internationally, the ‘boomerang effect’ brings it back to the attention of media in Japan.” (Sunda, 2015)

The politically apathetic image of Japanese youth could be influenced by systematic limitations from government and education. Therefore, to shift their image and pursue globalization in the future; as young adults in Japan, they will have to be the ones to take a step out of their comfort zone to initiate the move of exploring those topics.

### For the future

Whether it was a coincidence or not, it is interesting to point out that just by looking at the timeline, youth seem to stand up following a tragedy. In the case of Zenkyoto, the anti-Vietnam War was one of their common grounds for their unity. With SEALDs, they were initially formed due to the issue of Article nine in the Japanese Constitution. This could indicate the rise of student movements as Japan emerges from this global pandemic. In a way of a continuance of SEALDs activism, demonstrating the relevance of politics in youth’s daily lives should be the first step to increase youth engagement in politics, which can result in more voters and conversations about social issues as well. Moreover, having their

own space for self-governance for further improvements with creating a structured community and valuing inclusivity, and finding a larger scale of common ground in activism will be important aspects to gain more participants in sustainable activism in Japan.

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# Studies on the Innovative Application of Immersive Virtual Reality in Medicine: The Possibilities of Full-Dive Virtual Reality

Misaki Tatsumi

Belmont High School, United States  
misakisak@icloud.com

## Abstract

In *Sword Art Online* (SAO) animation and light novel, Full-Dive Virtual Reality (FDVR) was realized in 2022 but it is a dream technology in our world. The brain is sometimes expressed as a black box since it has many unknown mechanisms and functions, and it is difficult to investigate the real human brain *in vivo*. However, various technologies for neuroscience are being developed rapidly, for example, related software or hardware which enable to analyze brain activities with device to realize FDVR. At the same time, the applications of virtual reality (VR) have been highly expected not only in the entertainment world but also in the medical field. Although VR use for surgical treating has already become popular with robotics, we must much more innovate medical applications for treatments and safety. This study demonstrates the possibilities of VR and FDVR. First, I will investigate the development in VR and the feasibility of VR application in pediatrics and then elucidate FDVR possibility and difficulty, with which I would like to grapple for future trials.

## Introduction

Full Dive Virtual Reality (FDVR) is from a Japanese light novel and Anime series, *Sword Art Online* (SAO) written by Reki Kawahara in 2009 (TV Animation, n.d.). It is a futuristic technology designed to create a Virtual Reality Massive Multiplayer Online Role-Playing Game (VRMMORPG). You can go through an immersive

virtual reality with a wearable device, like a helmet, receiving external signals for user interaction between the brain and a computer. It looks like scuba diving; we jump into the sea world with all of our senses. This concept is very attractive for gamers as well as developers, but it is still a dream. The expansion of the application is highly expected, especially in the medical field. FDVR is akin to virtual reality (VR), but the system is entirely different. FDVR needs more advanced technology which enables not only to understand electroencephalograms precisely but also to make sensory feedback to the brain. Some of the Brain-Computer-Interfaces (BCI) have been developed to perceive brain activities. Though these BCI developments are on the way, conventional VR is also revamped for its quality challenges for medical use. First, I will investigate the feasibility of the application of VR in the medical field and then elucidate FDVR's possibility and difficulty for future trials, which I would like to challenge.

## Methodology

The use of VR in the medical field, primarily pediatric, electroencephalogram (EEG) and the potential use for the sensory disorder, and the possibilities of obtaining FDVR are investigated and discussed. The searches were done by using Google Scholar through Google search engine in English and Japanese. The searched terms are listed in Table 1, which includes some related words with VR, FDVR in medicine.

TABLE 1: Search terms

	English Terms	Japanese Terms
1	Full Dive Virtual Reality	フルダイブ技術
2	Sword Art Online, NerveGear	ソードアートオンライン、ナーヴギア
3	Sword Art Online Full Dive system	ソードアートオンライン、フルダイブ技術
4	Virtual Reality and Medical use	バーチャルリアリティと医療応用
5	Pediatric and Virtual Reality	小児科とVR
6	Pediatric Pain	
7	VR and Pediatric Mental Health	VRと小児患者のメンタルヘルス
8	Brain-Computer Interface	
9	VR and Psychology	VRと
10	VR and Pain	VRと痛み
11	Pediatric Mental Health	小児科とメンタルヘルス
12	Sensory disorders	感覚器障害
13	Cochlear implant	人工内耳
14	Visual impairment and treatment	視覚障害と治療法

TABLE 2: Number of references used by category. The number in parentheses is for Japanese.

	Paper	Article (blog)	Video (YouTube)	Total number
Full Dive	0 (0)	6 (5)	0 (0)	6 (5)
Electroencephalogram	1 (0)	7 (5)	3 (0)	11 (5)
VR and Pediatric	7 (1)	1 (1)	0 (0)	8 (3)
VR technology	3 (0)	2(0)	1 (0)	6(0)
Pediatric Patients	2 (2)	0 (0)	0 (0)	2 (2)
Sensory Disorder	7 (4)	0 (0)	0 (0)	7 (4)
<b>Total number</b>	<b>20 (7)</b>	<b>16 (11)</b>	<b>4 (0)</b>	<b>40 (19)</b>

The references collected for this study were arranged according to the following genres: Full Dive Virtual Reality, Electroencephalogram, VR and Pediatric, VR technology, Mental Health, and Pediatric Patients, Sensory disorders. The order makes it easy to correlate the facts between different things. In each reference, the information is distinguished by how relevant and irrelevant. (e.g., it excludes the cause of sensory disorder but includes the treatment).

All searches were done with the keyword listed in Table 2. Though there are not so many, it is thought to be enough coverage for this study.

However, much improvement remains for the following study.

### Results

This part is divided into four parts, (1) Virtual Reality, (2) Virtual Reality and Pediatric Treatment, (3) Full Dive Virtual Reality and Electroencephalogram, and (4) Sensory Disorder and treatment.

#### (1) Virtual Reality

Virtual Reality (VR) is defined as "the computer-generated simulation of a three-dimensional image or environment that can be interacted with in a seemingly real or physical way by a person

using special electronic equipment, such as a helmet with a screen inside or gloves fitted with sensors" (Lexico Dictionaries, n.d.). The user gets through VR using output and input devices such as a headset, headphones, and controllers. The restriction of the user's movement decreases the quality of immersion feelings of VR. TESLASUIT (Teslasuit, 2020; Full body haptic feedback & motion capture tracking VR suit, 2021) is a full-body haptic suit and training solution for physical VR experiences (Figure 1). The haptic sensation is requisite for enhancing the immersion. The suit generates feedback to any part of the body area from gentle touch to feelings of physical exertion and temperature. It outputs haptic feedback from VR (touch feedback is similar to an abdominal muscle pad) which can be used for training or



FIGURE 1: TESLASUIT is a full body haptic suit and training solution for physical VR experience. Author's own figure created in reference to TESLASUIT (2021).

learning how to use their body efficiently. It is incredible technology because touch feedback makes it easier to control and demonstrate sensitive movements. If you do not have sensitive haptic feedback, you will not be able to move normally. Fig. 2 shows an example of the importance of feedback when grabbing a cupcake. In Fig. 2a, a person getting feedback about the distance between the hand to the cupcake can approach it in the proper position.

Still, in Fig. 2b, the hand could not reach it without the visual information because the brain could not calculate the correct distance for the approach. Figs. 2c and 2d demonstrate shockingly different results without the proper haptic feedback. The person must grab the cupcake with the correct amount of force. Otherwise, exerting too much energy when grabbing makes the cupcake compact, as seen in Fig. 2c. The meticulous feedback cycles with fine tactile signals from your hands fulfill your brain's will to make you happy with the cake to eat.

Besides sensory, we need body ownership in VR for a high-quality immersive experience, i.e., positional information about our body parts. In the study (Kondo et al., 2018; Yin, 2018; Urushih, 2018), humans can feel body ownership for a virtual body at least when they see their arms and legs, but still, it is weak. They feel real pain to the virtual body that the person feels ownership of, but it only happens when they experience something so hard or impressive, like a knifed imaginary body. In another study (Kanaya et al., n.d.), a person felt stimulation, including illusory thermal sensations for their prosthetic hand made of rubber when the person observes hot water poured on the rubber hand, called rubber hand illusion (RHI). It is a crucial term for developing VR.

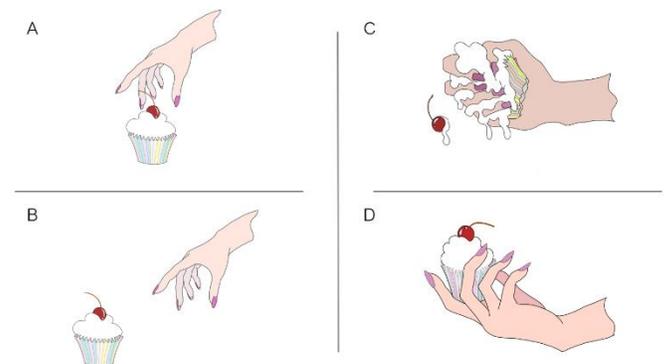


FIGURE 2:  
a. A hand in the right approach to pick up the cake  
b. A hand in the wrong place resulting in failing to touch the cake  
c. A hand in the right place without touch feedback culminating crashing the cake

d. A hand in right approach and place with proper visual and tactile feedback to succeed in holding the cake

### *(2) Virtual Reality and Pediatric Treatment*

Some papers indicate the effectiveness of reducing pain during the treatment or chronic pain. Also, it could be applied to mental diseases. The study (Won et al., 2017) reviews recent literature in pediatric virtual reality in procedural and anxiety, acute and chronic pain, and some rehabilitation applications. Participating in the virtual environment featuring a wintery scenario, called "SnowWorld" during painful repetitive dressing changes in patients with burn wounds reduced 27-44% for acute and procedural pain. It also shows success in lessening procedural pain and distress related to intravenous (IV) placement and other needle-related procedures (note: it was not immersive VR). In chronic pain, it demonstrated a significant change in complex regional pain syndrome (CRPS) and phantom limb pain (PLP), which indicates the effectiveness for adults. In addition, it revealed the benefits of the neurorehabilitation application of VR.

Another study (Eijlers et al., 2019) demonstrated that VR significantly impacts pediatric pain and anxiety during medical procedures, especially for younger children. It is hardly effective for adults for the quality of VR used. Furthermore, it can be used to reduce anxiety before the operation (Ahmadpour et al., 2020; Gold et al., 2021) for example, "Doc McStuffins: Doctor for a Day" (it is a VR experience program done before the operation for children to introduce operation room and tools).

To exhibit higher quality experience and effectiveness, we need to think about the best content for children's treatment. There are many types of VR content to have real-life-like experiences (also includes fighting games) (Nuhei, 2003).

Examples of VR applications:

- Let's go to the zoo

- VR school (joining the class from the hospital bed)
- VR miniature garden (creating a miniature garden with pictures of humans, animals, plants, etc.)
- VR cast (talk with characters in the VR in real-time).

These terms show that the emotion will change with the detail of VR.

Long-term treatment like childhood cancer provides numerous challenges and sources of stress for patients and it removes children from their everyday social environment and previously enjoyed activities. Therefore, VR can be used for mental health care (Tennant et al., 2020), such contents listed above.

### *(3) Full Dive Virtual Reality and Electroencephalogram*

FDVR is stated that electronic equipment (e.g., brain-computer interfaces) reads EEG and gives feedbacks (e.g., sensory feedback also emotional) to the brain; it would be done without using any parts of the body, excluding our brain. It is forwards compatible with VR but remains the state of dream technologies (Eisenberg, 2021). In FDVR, there are two types, invasive type and noninvasive type, which is to put the electrode directly into the brain or not (Kawakatsu, 2021; Editorial, 2019).

EEG is a wave-like signal in which electrical activities in the brain are recorded by electroencephalography called brain-computer interfaces (BCIs) (National Science Foundation, 2015; What is an electroencephalogram?, n.d.; Wikimedia Foundation, 2021). There are some examples of practical use of reading EEG (Directly decipher sentences from the brain activity of people who cannot speak, 2021; Birbaumer & Cohen, 2007; Kubota, 2021).

Example 1: the examiner is a 36 years old man who had a stroke at the age of 20, got articulation disorder, and cannot move the head, neck, arms, and legs from its sequelae. In this examination, he

conversed for the first time over 15 years. He usually talks with the stick on his baseball cap to point out the alphabet on the paper (US Scan Francisco (UCSF), 2021). First of all, BCIs and artificial intelligence (AI) made it possible to read EEG and generate it into the words at a maximum of 18 words per minute, an average accuracy of 75%. It was an invasive type that stings electrodes directly into the brain. Before making it possible, they took a few months to record the electric signal into the computer to educate AI.

Example 2: A car demonstrated that it could be controlled by visualizing cubic movements in its head (Emotiv's new neuro-headset, 2014). It means you cannot move a car when you visualize the car moving or recite to move; it moves only when you visualize the cube moving for now. It works by scanning your brain for signals using the Emotiv EEG device on your head.

If the technologies in the two examples are used practically, more things are possible to control with our brain without the presence of physical forces.

#### *(4) Sensory Disorder and treatment*

The research was primarily done about hearing and sight impairment. First, an artificial cochlear implant is a device that duplicates the inner ear cochlear with engineering technology and complements patients' hearing by putting it within the inner ear cochlear (Kaneko, 2016) (Fig. 3).

This device is a bypass information processing system that decomposes sound information into frequencies and transmits it as an electrical stimulus to the cochlear nerve. The patients do not hear the same as the original human hearing system, so they need special training. Thus, the implant is a great way to deal with hearing impairments, but it is still difficult to hear naturally. Also, surgical implantation sometimes causes infection complications, so some patients were forced to remove it (Brkic et al., 2018).

Cochlear implanted children's levels of hindrance are different so that corresponding individual treatments are needed. For example, talking with

one person is possible, but it is not easy to talk with more than one person or listen to someone talking in the crowd, which estimates that each cochlear implanted child needs long-term rehabilitation with doctors, speech-language-hearing therapists, and teachers (Moroto & Naito, 2021). Moreover, the teachers want to have a training session to learn about involvement, the ways to communicate children with disability (National Institute of Special Needs Education, 2021).

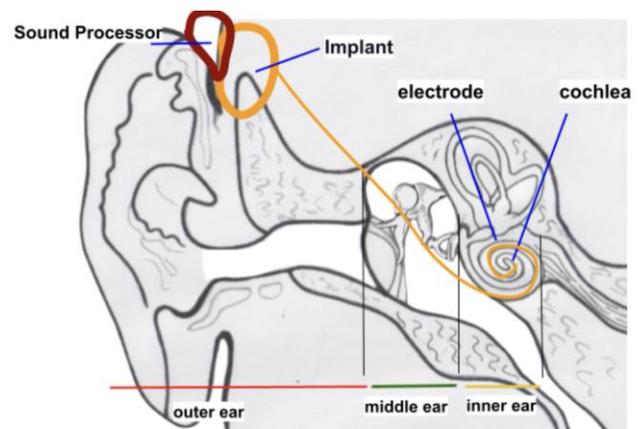


FIGURE 3. Anatomical demonstration of artificial cochlea implant in the ear

Second, an alternative device for the treatment of eye impairment. The system comprises custom-designed headgear with a camera and wireless transmitter, a vision processor unit and software, and a set of 9x9 mm tiles that are implanted into the brain (Opening eyes to a frontier in vision restoration, 2020). The small tile embeds into the brain receives the information from a camera and stimulates the brain, and it helps improve or resurrect the sight.

#### **Discussion**

This study shows what we can do now and the limit to realize practical use of VR/FDVR with existing techniques.

VR has pros and cons; one of the pros is that we can exercise our bodies for real and go to the VR world simultaneously with corresponding feedbacks, but it may become a con. When the

person cannot give a signal to the VR system (what they want, controlling an avatar in the video game) or cannot receive the feedback, the sense of presence becomes poor because VR's feedback depends on the sense of sight and hearing a lot. Also in real experience, we usually obtain full-scale body information against the environment as feedback as five-senses. Furthermore, to perceive touch feedback, you need to wear a device (Full body haptic feedback motion capture tracking VR Suit, 2021; Charlton, 2021). Most of the quality of experiences is compensated by audio-visual responses to use's action. Those haptic feedbacks make it possible to do detailed and vivid sensation for humans.

This research encourages the use of VR within the treatments for pediatric patients. In the investigation, VR is effective for reducing pain, stress (anxiety), and the amount of medicine. Nevertheless, examinations are not enough to prove that VR is a reliable treatment for those users.

To actualize FDVR, both input and output have to work well at the same time; input is the sense of touch, sight, hear, smell, tastes (the last two have not been mentioned in any references and the result), and output is expressing (including face, conversion, etc.) and moving body in avatar. For that sake, we need to develop plenty of devices. At this moment, we could have wireless electronic implants input to the sight from the camera (Liu et al., n.d.). In the device development process, the developer needs aiming to monitor each nerve cell level and analyze its change. Thus, I came up with the idea of computed neural circuit encephalogram (CNCE) using the similar technology of computed tomography (CT); its technology can be used to detect much more specific activities of the neural networks by calculating based on the stored AI processed algorithm.

Also, skills to remove the noise of electromyogram (EMG) from CNCE is necessary; that is why we collect the noisy data of EMG while moving the body. In addition, we need to send information

directly into the brain; the cochlear implant is close to that, i.e., sends the electric signal into the cochlear nerve but not directly into the brain. Even though we cannot convey the stimulus to the brain directly, the sounds implanted-patients hear might be electric-like sounds, entirely different from what we hear. To be used to or understand that sounds need much rehabilitation with a special therapist. If the rehabilitation can be done in FDVR, it will be possible to deploy high-quality-language treatment to everyone who needs it.

Requirements for the effective FDVR:

- No pain to use, no blood (noninvasive FDVR system)
- Lightweight
- No risk of infection
- Everyone can use it for treatment (universal style and low-priced)
- High-speed connection to the Internet
- High quality sensor
- Seemingly real and intriguing content for the users

These requirements would make FDVR more useful to provide a high-quality experience.

I suggest that if FDVR can access the brain directly, it helps to accelerate brain plasticity to improve human life. It means it could rebuild neural circuits with FDVR system; in other words, it may create new memories in FDVR world to replace the bad memories with happy ones. FDVR needs output signals from our brain to control the avatar and input signals to the brain for better output as a feedback system. At the same time, it intentionally enables us to cut or add the signals by creating the same environment as the patients feel. It could provide opportunities to experience how difficult the patients feel and check how much they improve with the treatment.

There were some limitations for this investigation; the lack of information on FDVR and VR use in pediatrics, but it shows the benefit of utilizing it as an additional treatment in the medical field. It

would also work for adults if its quality of reality and contents increases.

To conclude, there is enormous room for improvement and development in VR/FDVR. They could expand what we can do in this world, especially in the medical field.

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# Investigating the Sequence Elements that Affect the Translation Efficiency of the Fungal Pathogen *Histoplasma Capsulatum*

Annika Viswesh

Palo Alto Senior High School, United States

annikaviswesh@gmail.com

## Abstract

Histoplasmosis disease is caused by the dimorphic switch of the *Histoplasma capsulatum* fungus. Predicting the Translational Efficiency (TE) for *Histoplasma capsulatum* will lead to techniques that can regulate its protein production and thereby help in the treatment of Histoplasmosis. However, what sequence elements in the mRNA determine TE in *Histoplasma* is not well understood. The 5' Untranslated region (UTR) of 4981 genes common to 4 strains of *Histoplasma* were explored to identify the correlation between the longest 5 Upstream Open Reading Frame (uORFs) with start codon ATG, length of the 5' UTR, the energy of constrained secondary RNA structure, CG-to-ATG ratio and TE, using Wilcoxon tests, normal distribution plots, and Area under the receiver operating characteristics (ROC) curve. Subsequently, using all these sequence elements as features, four computational models were developed using different machine learning algorithms to predict TE. The results demonstrate that the maximum length of uORF with start codon ATG and the CG-to-ATG ratio have the best correlation to TE with the highest Area Under the Curve (AUC) amongst all sequence elements at 0.74 and 0.79, respectively. Also, computational model created using Random Forest outperformed other models to best predict TE with an AUC of 0.85. This research helped identify a set of sequence

elements that affect TE in *Histoplasma capsulatum* and also showed that computational models can be created for predicting the TE of *Histoplasma*.

*Keywords:* *Histoplasma capsulatum*, *Histoplasmosis*, *machine learning*, *sequence elements*, *translation efficiency*

## Introduction

*Histoplasma capsulatum* is a fungus that has a yeast form and a mold form (Gilmore et al. 2015; Inglis et al. 2013). They reside in soils. They are commonly found in the Ohio and Mississippi River Valleys, as well as in other parts of the world (Bahr et al. 2020). People typically inhale the microscopic spores when the environment in which *Histoplasma* fungi lives in, is disturbed (Centers for Disease Control and Prevention, 2021). When the microscopic spores in the mold form enter a human body, the fungus performs a dimorphic switch, turning into yeast (Gilmore et al. 2015; Beyhan & Sil 2019). In its yeast form *Histoplasma capsulatum* causes a disease called Histoplasmosis. Each year, up to 250,000 people in the U.S. are found to have Histoplasmosis (Fayyaz et al. 2020). The disease does not spread because of person-to-person contact (Stöppler 2020; Beyhan & Sil 2019).

Symptoms of Histoplasmosis include fever, cough, fatigue, chills, headache, chest pain, and

body aches (Kauffman 2007). The spectrum of the infection includes mild, acute, chronic, and life-threatening sepsis (Kauffman 2007, Wheat et al. 2000). Although the disease is not easy to diagnose, the disease mostly goes away in a few weeks (Kauffman 2007, Knox & Hage 2010). When it becomes acute or chronic, antifungal medication is required (Knox & Hage 2010). Chronic pulmonary histoplasmosis if left untreated can have a mortality rate of 50% and with treatment it can have a mortality rate of 28% (Stöppler 2020).

Doctors diagnose Histoplasmosis through CT scans and X-rays (Stöppler 2020; Wheat et al. 2007). There is no vaccine against the disease. There are no drugs that specifically target the disease (Stöppler 2020; Wheat et al. 2000). Doctors recommend common antifungal medications of Itraconazole and amphotericin B for Histoplasmosis; patients with severe Histoplasmosis undergo treatment for several months (Wheat et al. 2000). Besides Histoplasmosis, Ocular histoplasmosis is most common in people who are exposed to the fungus at a very young age (U.S. Department of Health and Human Services, 2020). It happens when the fungus spreads from the lungs to the eyes. Early diagnosis and treatment are essential in preventing vision loss.

### *Existing State of Research*

The Sil lab in the University of California - San Francisco (UCSF) has used mRNA sequencing and ribosomal footprinting to calculate the Translational Efficiency (TE) for each gene in four different strands of Histoplasma: G217B, HcH88, HcG186AR, and HcH143 (Gilmore et al. 2015). TE is measured as the footprint counts over mRNA counts. Researchers use TE as a key tool in measuring changes in RNA levels between different cell states. It is used as an indicator of protein production. By observing the sequence of the genes, the researchers have hypothesized that the immense variance in translational

efficiencies for long and short DNA sequences could be because tRNA reads the stop codon prematurely after reading the start codon, which may result in the entire DNA message not getting translated accurately (Gilmore et al. 2015; Beyhan & Sil 2019). Even though the researchers noted several biomarkers that “may” influence TE, they have not found the actual list of biomarkers or sequence elements that best correlate with TE (Gilmore et al. 2015; Arribere & Gilbert 2013). Also, researchers have not figured out how they can use biomarkers to predict the TE computationally.

### **Goals**

The goals of this research are the following:

- Identify sequence elements that affect TE in the yeast form of Histoplasma.
- Create a computational model to predict the TE in the yeast form of Histoplasma.

### **Methodology**

Data from HistoBase database in the Sil Lab, UCSF was used in this study. Python code was developed to extract data from the database for 4 strains of Histoplasma, each with over 6500 genes. The **4 strains** were G217B, HcH88, HcG186AR, and HcH143. Then, data was filtered to contain similar genes across 4 strains which resulted in **4891** genes. Subsequently, different sequence elements in the 5' Untranslated Region (UTR) were examined and its correlation to TE was determined using normal distribution curves, scatter plots, Wilcoxon tests, and Receiver Operating Characteristics (ROC) curves.

The following sequence elements were investigated to determine their correlation to TE:

1. **Length of the Upstream Open Reading Frames (uORFs):** The uORFs were chosen because in eukaryotic mRNAs, the translation of the protein requires the translation of uORFs (Gilmore et al. 2015). These biological structures aid in repressing or non-repressing the gene, which can lead to lower or higher

TE values respectively (Gilmore et al. 2015; Arribere & Gilbert 2013). The maximum length of the uORF was chosen because we hypothesized that greater length could have a higher influence on the initiation of translation. To get the largest length of the uORF, code was developed to extract the start and end points of the different uORFs, and their difference was taken for the 4981 genes. To determine if there is a correlation between TE and length of the uORFs, a scatter plot and a box plot were plotted. A Wilcoxon test was used to verify the results. Code was developed to calculate the true positive rate (TPR) and the false positive rates (FPR) using the data from the scatter and box plots and Receiver Operating Characteristic (ROC) curve was generated.

$$\text{FPR} = (\text{False Positives}) / (\text{Total Negatives})$$

$$= (\text{False Positives}) / (\text{False Positives} + \text{True Negative})$$

$$\text{TPR} = (\text{True Positives}) / (\text{Total Positives})$$

$$= (\text{True Positives}) / (\text{True Positives} + \text{False Negatives})$$

The ROC plot was analyzed to determine if TE was affected by length of the uORFs.

2. **Secondary RNA structure:** The energy of constrained secondary RNA structure was studied to see if secondary structures such as hairpin or loops could interfere with translation. A ROC curve using the energy of the constrained RNA structure against TE was plotted to determine if there was any relation between them.
3. **Length of the 5' UTR:** 5' UTR is the region directly upstream of the start codon. Previous studies show that genes that had a low length of 5' UTR sometimes had a low maximum length of uORFs, and those genes are translationally repressed (Gilmore et al.

2015). The length of the 5' UTR as a predictor of TE was evaluated by plotting a ROC curve.

4. **CG to ATG ratio in uORFs:** In the nucleotides, CG has 3 hydrogen bonds while AT has 2 hydrogen bonds. Since the RNA unzips the DNA by breaking Hydrogen bonds, the effect of CG to ATG ratio on TE was evaluated using a ROC curve.

After examining the individual sequence elements and their relation to TE, the effect of the combined sequence elements was used to predict TE. Derived features consisting of the sum of the top five uORFs and the ratio of the sum of the top five uORFs to the length of 5' UTR were also used as part of the combined input. Computational models were built using Linear Regression, Lasso Regression, Decision Tree Regression, and Random Forest which are four different supervised machine learning (ML) algorithms to evaluate how well the combined features contributed to predicting TE. High variance in the input data was mitigated using standard scaler function of Sci-kit learn Python library. The standard scaler transforms the data to ensure that the standard deviation of the data is one and the mean of the data is zero. Input data was randomly split into training, test, and validation sets in 70:20:10 ratio. 10-fold cross validation was used while training the data to build the computational models. ROC plots, root-mean-squared-error (RMSE), and r-squared score were used to compare the effectiveness of the different ML

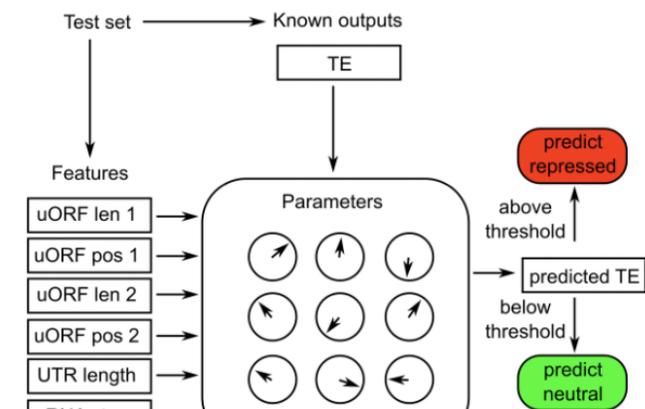


FIGURE 1. Workflow for building the computational models using Machine learning to

models to predict TE. Figure 1 shows the workflow for building the computational models.

## Results

The frequency distribution of TE values using a logarithmic scale is shown in Figure 2. The correlation between TE and length of the uORFs was visualized using a scatterplot as shown in Figure 3a. The scatter plot of maximum uORF lengths using ATG as the start codon vs. TE values is shown in Figure 3b. The Boxplot of the maximum length of a uORF across different genes is shown in Figure 4. The true positive (TPR) and the false positive rates (FPR) were calculated (Table 1) computationally using a threshold value of -2 and are plotted to generate a Receiver Operating Characteristic (ROC) curve in Figure 5a. The ROC plot of energy of the constrained RNA structure vs. TE is shown in Figure 5c. The ROC plot of the relationship between length of the 5' UTR and TE (in blue) using True Positive Rate (tpr) vs False Positive Rate (fdr) is shown in Figure 5d. The ROC plot of the relationship between CG/ATG ratio and TE (in green) using True Positive Rate (tpr) vs False Positive Rate (fdr) is shown in Figure 5e.

	Feature $\geq$ Threshold	Feature $<$ Threshold
$\log_2(\text{TE}) < -2$	TP	FN
$-2 \leq \log_2(\text{TE}) < 2$	FP	TN

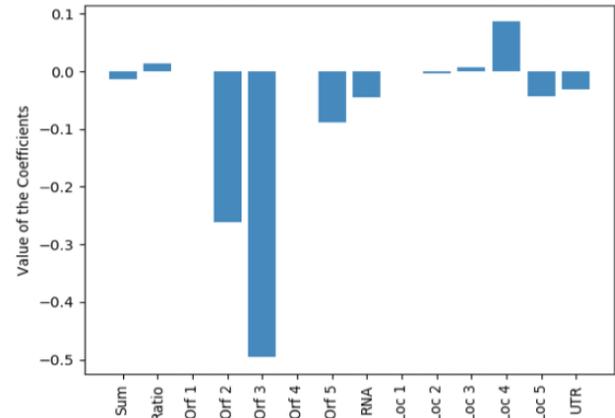
Table 1. The confusion matrix for the classification of TE prediction

To evaluate the quality of the results of the various ML algorithms, three standard metrics were used: ROC curves, root-mean-squared-error (RMSE), and r-squared score.

Linear regression gave a training RMSE of 1.65, a testing RMSE of 1.67, a testing r2 score of 0.23, and a training r2 score of 0.27. Figure 6a shows

the coefficients of the features used in the linear regression algorithm.

Lasso regression gave a training RMSE of 1.63, a testing RMSE of 1.72, a testing r2 score of 0.16 and a training r2 score of 0.23. Figure 6b shows the coefficients used for Lasso regression algorithm. Figure 5g compares the ROC plots of the Lasso Regression with the maximum length of



the uORF.

Figure 6a. Coefficient values of the features used in

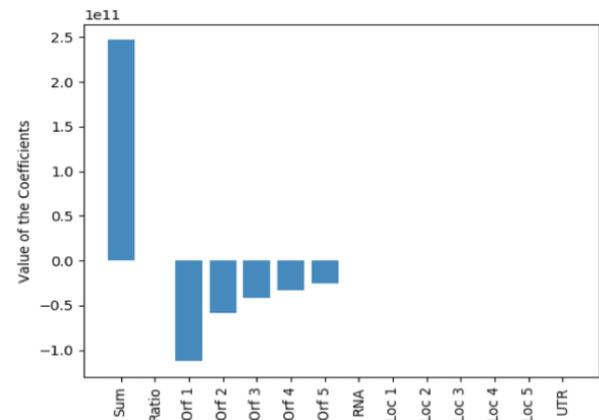


Figure 6b. Coefficient values of the features used Lasso Regression

The Decision Tree Regressor gave a training RMSE of 1.64, a testing RMSE of 1.79, a testing r2 score of 0.2, and a training r2 score of 0.23. Figure 5h compares the ROC plots of the Decision Tree to the maximum length of the uORF.

Random Forest gave a training RMSE of 1.37, a testing RMSE of 1.39, a testing r2 score of 0.47,

and a training  $r^2$  score of 0.46. Figure 5i compares the ROC plots of Random Forest with the maximum length of the uORF. Figure 7 shows the comparison of the various ROC plots with each other.

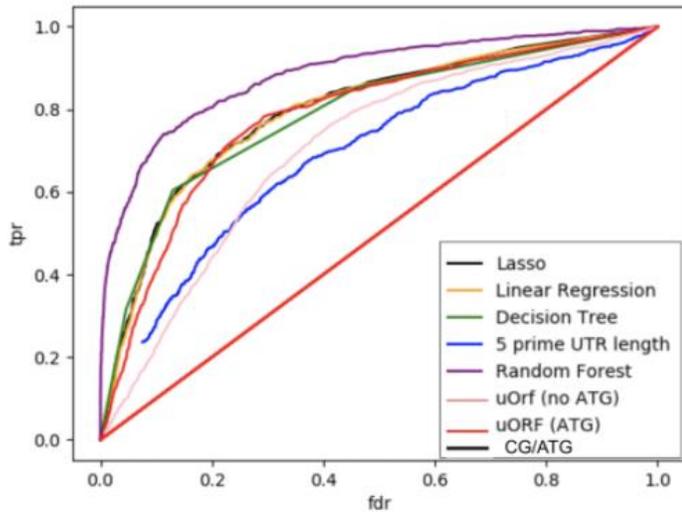


Figure 7. Relative comparison of the ROC plots for various learning models

### Discussions

Figure 2 indicates that the frequency distribution of TE is not a normal distribution. Under ideal conditions, the number of footprint counts will be equal to mRNA counts but the graph indicates a spike in the values between -2 and 2.

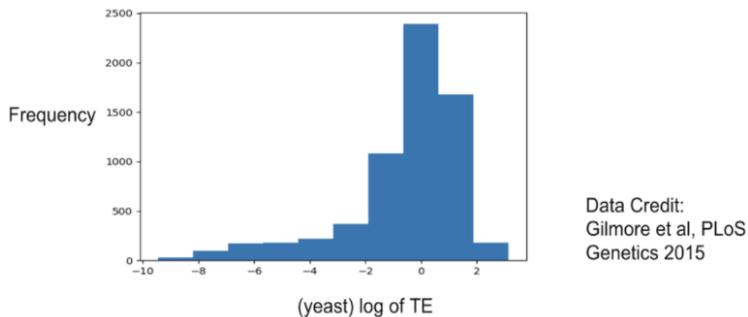
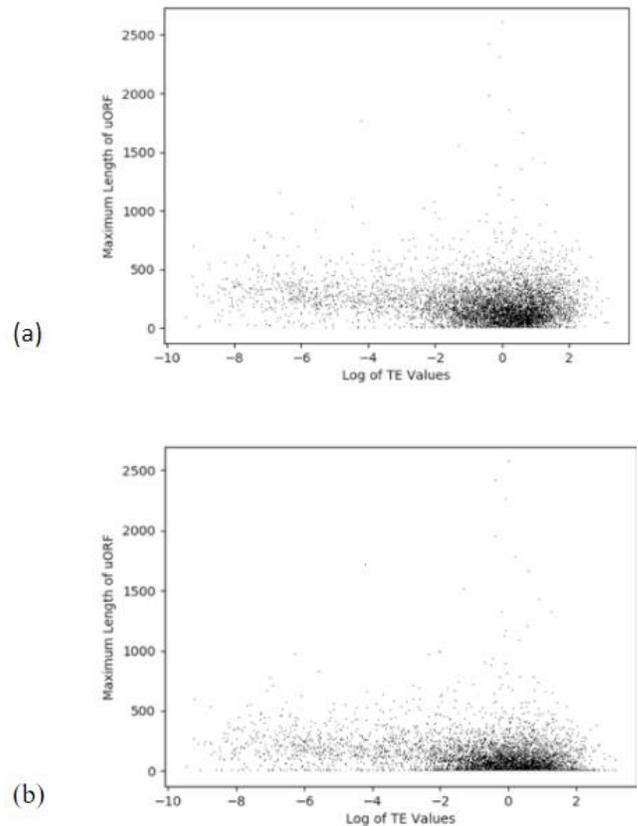


Figure 2. Frequency distribution of TE values

### Upstream Open Reading Frames (uORFs) vs. TE

Figure 3a depicts a weak negative correlation between the TE values and maximum length of the uORFs, where each dot represents a gene common across all four strains of Histoplasma:

HcG217B, HcH88, HcH143, HcG186Ar. Figure 4 conveys that the length of the largest uORF indeed significantly distinguishes translationally repressed genes from neutral genes. This was verified through the Wilcoxon test, in which the P-Value was  $2.2e - 16$ . Based on Figure 3a and Figure 4, a threshold value of -2 was chosen to



generate a Receiver Operating Characteristic (ROC) curve in Figure 5a.

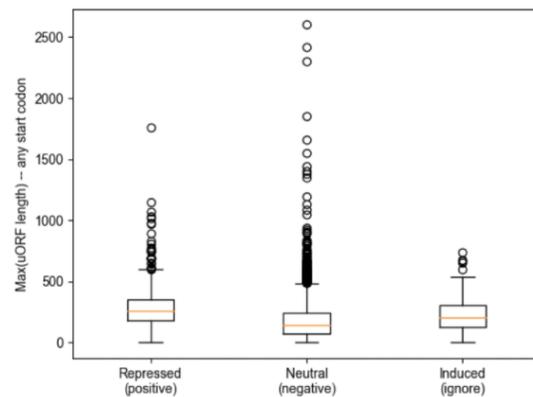


Figure 4. Boxplot of the maximum length of a uORF across different genes

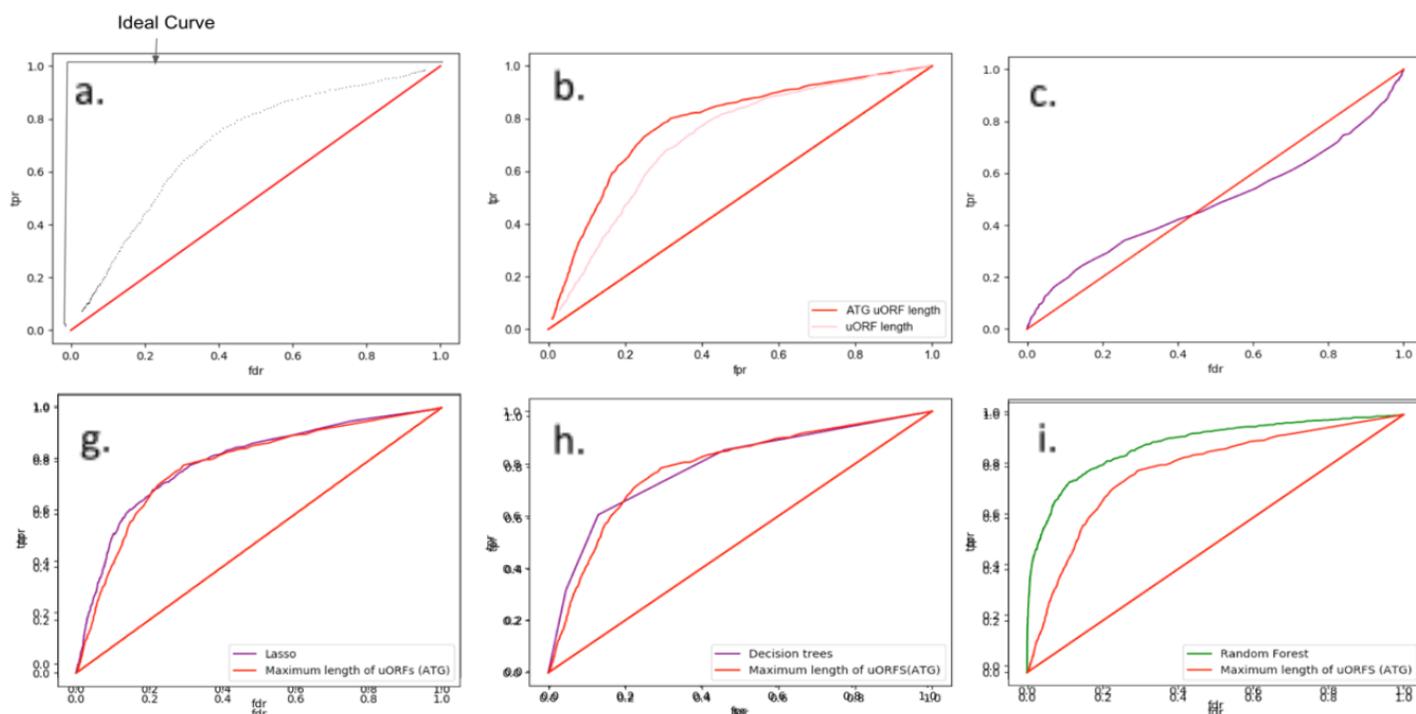


Figure 5. ROC plot showing the relationships between a feature/predictor and TE | a) maximum uORF length for any start codon (in black dots) | b) maximum uORF length with ATG start Codon (in red) | c) energy of constrained secondary RNA structure (in purple) | d) length of the 5' UTR and TE (in blue) | e) CG/ATG ratio (in green) | f) Linear regression (in green) | g) Lasso regression (in purple) | h) Decision Tree Regressor (in purple) | i) Random Forest Regressor (in green)

Analysis of the ROC plot of the maximum length of uORF vs. TE has area under the curve (AUC) of 0.68 which predicts TE better than mean value. It shows that the maximum length of uORF works as a good predictor of TE (i.e., the genes that were repressed have a correlation with maximum length of uORFs). However, in this case any start codon was used when calculating the maximum length of the uORF. ATG (i.e. AUG) is the start codon of mRNA as it is first to undergo translation after transcription. When the analysis was repeated using the ATG start codon (vs. the use of any start codon in the previous analysis), it was observed that there still existed a weak negative correlation between the open reading frames and the translational efficiency (Figure 3b). However, the ROC for this scenario with only ATG as start codon, revealed a bigger area under the curve with AUC = 0.74 (Figure 5b) compared to the previous ROC curve. Therefore, the maximum

length of uORF with start codon ATG correlates better to TE.

#### *Secondary RNA structure vs. TE*

The ROC plot (Figure 5c) of energy of the constrained RNA structure vs. TE showed that RNA structure does not correlate well with TE. In fact, the second half of the ROC plot conveys that the probability of predicting TE is less than the probability of randomly flipping a coin.

#### *Length of 5' UTR vs. TE*

In the ROC plot (Figure 5d) of the length of 5' UTR vs. TE showed that the curve of the uORFs with start codons of "ATG" (in red) performs better than the length of the 5' UTR (in blue). Nevertheless, the correlation between TE and length of 5' UTR with AUC = 0.63 was better than the average value.

### *CG to ATG ratio in uORFs*

The ROC plot (Figure 5e) with AUC = 0.79 shows that there is a very good correlation between the CG/ATG ratio (in green) and TE and it performed better than uORFs with start codons of "ATG" (in red).

### *Linear Regression*

From Figure 6a, we can infer that low R-squared values are due to high variance in the data. The coefficients also indicate that the sum of the top five uORFs as well as the maximum length of the uORF per gene has a high correlation with TE. Figure 5f compares the ROC plots of the Linear Regression with the maximum length of the uORF. The ROC plot shows that Linear regression using all the features does slightly better with AUC = 0.75 than just using the maximum length of the uORF (AUC = 0.74).

### *Lasso Regression*

Since there is some difference between both the RMSE and the r-squared scores, Lasso model slightly overfits the data. Contrary to the Linear regression model, the sum of the top five uORFs and the maximum length of the uORF did not have a high coefficient value. Instead, the second and third largest uORF lengths had the highest coefficient values. The ROC plot in Figure 5g shows that Lasso regression (AUC = 0.74) performs the same as the maximum length of the uORF and does not add any better performance compared to Linear regression.

### *Decision Tree*

The algorithm slightly overfits because of the difference between the RMSE scores for training and testing. The ROC plot in Figure 5h shows that the Decision Tree (AUC = 0.69) performs worse than the maximum length of the uORF predictor.

### *Random Forest*

Unlike the previous algorithms, Random Forest performed substantially better with AUC = 0.85

(Figure 5i) compared to the maximum length of the uORF predictor.

### *Comparing all results*

The sequence elements CG to ATG ratio and maximum length of uORF with ATG as the start codon, each by themselves alone, gave the best performance with AUC at 0.79 and 0.74 respectively and therefore demonstrated the best correlation with TE for single features. The uORF with ATG as the start codon acts as a better predictor than uORF with any start codon because the former (relatively speaking) potentially increases the likelihood of translation starting before it reaches the main functional ORF. The length of 5' UTR to predict TE (AUC = 0.63) was not a good predictor of TE compared to the above two sequence elements. The biological reason why the length of 5' UTR predictor is possibly worse than the largest uORF predictor could be that the length of a UTR and the maximum length of uORF are not well correlated with each other, i.e. you can have a long 5' UTR region with many small length uORFs in it. The Secondary RNA structure was the poorest predictor of TE possibly because the positions of the hairpins are probably not ideal to influence the initiation or repression of translation.

The different learning models can be assigned to the categories of 1) Single feature (uORF-no ATG, 5' UTR length, uORF - ATG) 2) Multiple features (Decision Tree, Linear, Lasso) and 3) Ensemble of multiple features (Random Forest).

The RMSE test and train values for the different computational models built using the combined sequence elements to predict TE were comparable and had little to no overfitting. The low r-squared values in all models indicated that the data has high variance. Lasso regression model (AUC = 0.74) and Linear regression model (AUC = 0.75) performed comparably to the maximum length of uORF with ATG as the start codon (AUC = 0.74) and CG to ATG ratio (AUC = 0.79). Decision trees model performed slightly

worse with AUC of 0.69. Random forest model performed best with AUC at 0.85 and had lowest RMSE of 1.37. The ensemble method of Random Forest works better than the individual Decision trees model because the individual model tends to make different types of errors on the subset of features chosen, and many of those errors cancel each other out in the ensemble method (Géron, 2020). Overall, the combination of multiple features, except when using Decision Trees, yielded slightly better results compared to using single features while predicting TE. This is to be expected as a model with multiple features has more information in building the decision boundary of a classifier.

The features and methods used in the prediction of TE in *Histoplasma capsulatum* can be applied to other single-cell eukaryotic organisms to improve our insight into how the sequence elements in the 5' UTR affects translation in other eukaryotic organisms. This would also make the findings from this research useful in the research of other diseases, not just Histoplasmosis.

## Conclusions

This research was the first to discover two sequence elements, CG to ATG ratio and maximum length of uORF with ATG as the start codon, in 5' UTR of mRNA that affect the TE in *Histoplasma capsulatum*. This research was also the first to develop four computational models for predicting TE of *Histoplasma* using the combined sequence elements. The recommendation is to use the computational model developed using Random Forest for predicting TE. This research improves our understanding of the sequence elements in the 5' UTR affecting the TE of *Histoplasma capsulatum*. In the future, similar features and methods can be used to predict the TE in other single-cell eukaryotic organisms which can improve our understanding of the translation process in other organisms. Also, in the future, the computational methods used in this research can be extended to use deep learning methods and

clustering methods, and their results can be compared with existing models to see if they can improve the predictions.

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# The Role of Neuroeconomics in Advertisement: a Systematic Review

Erin Wong

Great Neck South High School, United States

erinwong772@gmail.com

## Abstract

The integration of neuroscience into decision-making research started in the mid-1970s and its goal was to gain insight into the hidden sub-conscious cognitive processes that occurred during decision-making. This study analyzes the effectiveness of neuromarketing techniques, comparing them with traditional methods in order to shine a light on the role neuroeconomics plays in the advertising industry. The databases used for searching were PubMed, JSTOR, DOAJ, and Nature Communications. Experimental studies on healthy adult populations with full cognitive function were included. All the papers were screened by one person. Papers were screened according to abstract and title first, and then full texts were further screened for eligibility and inclusion. 201 studies were screened describing studies that applied neuromarketing methods in advertising campaigns with subjects that were healthy. 66 articles made it through to full-text screening for eligibility and 24 were selected for quality checking. Four papers were subject to in-depth analysis, and the main neuromarketing techniques used were discovered to be eye-tracking, biometrics, EEG, and fMRI with all of them having many advantages over traditional methods. Neuromarketing techniques can explain the correlations between regions of the brain and the implicated cognitive processes with much greater detail and depth than traditional methods, with the usage of fMRI being the best predictor of advertising success. One limitation was the inclusion of too few articles for analysis, and future

research could include companies modifying their ads in subtle ways using the existing knowledge to best target consumers.

*Keywords: neuroeconomics, advertisement, marketing, neuroimaging, decision-making*

## Introduction

Research in consumers' decision preferences in the industry has been done for quite a while, with interests going back to the early 1950s, where the goal was to mathematically model judgment and judgment and decision preferences (Hammond, 1955). During this time, research was done mostly using self-reported measures with traditional methods like surveys. Then, the use of neuroscience in decision research started to become popular in the mid-1970s (Payne, 1976) to early 2000s (Loewenstein et al., 2001). Now, the use of neuroscience and psychology in the field of decision-making research is coined "neuroeconomics" or "neuromarketing."

In neuroeconomics, the main techniques used are functional magnetic resonance imaging (fMRI), electroencephalogram (EEG), eye tracking, and biometrics, with fMRI and EEG being the most popular (Venkatraman et al., 2015). fMRI measures the changes in blood oxygenation in different parts of the brain during cognitive tasks which indicates the level of neural activity, while EEG reveals variations of electrical signals of cortical regions recorded at different frequencies (delta, theta, alpha, beta, gamma). Unlike the

other two techniques, eye tracking and biometrics do not directly measure brain modalities, with eye-tracking using an optical camera to determine the position of the pupil and cornea through infrared light. Similarly, biometrics measures physiological responses to stimuli through evaluation of heart rate, and skin conductance (Venkatraman et al., 2015).

Even with all the technologies and advancements that have been made in this field, there is still a lot yet to be uncovered and known. Studies have tried to identify the parts of the brain that are stimulated in the decision-making process and viewing of the advertisement to correlate it to already known functions of that specific part. For instance, research has been done on the neural activation of different structures of the prefrontal cortex, including the dorsolateral and ventromedial sections, and how it relates to a known function of the PFC, responsiveness (McFadden et al., 2015; Vezich et al., 2017). Another study has investigated the relationship in neural activity between other regions of interest (ROIs) including orbitofrontal, prefrontal, anterior cingulate cortex (ACC), cingulate motor (CMA), and parietal areas in attentiveness and memory retention for decision-making related to advertisements (Astolfi et al., 2008).

From the above sections, it is clear that neuroeconomics has had a profound impact on the advertisement industry, offering an unbiased look at what exactly happens in a consumer's brain during advertisements and after, in a shopping scenario. To further research in this avenue, a systematic review of the most vital findings of neuroscience in advertising must be done to summarize what has been achieved so far and how to proceed. To my knowledge, there are few recent systematic reviews conducted on this topic that discuss the same topic of neuromarketing's role in advertising through contrasting it with traditional methods, so in that sense, my study is novel.

### *Research question and objective*

This review attempts to answer the following question: How has neuroeconomics played a role in advertisement? This study discusses the role neuroeconomics plays in the advertising industry through comparisons between the effectiveness of neuromarketing techniques and traditional techniques.

### **Methods**

The target papers of this systematic review are populations that have data on the methods that neuroeconomics employ in advertisement, its effects, and comparison between traditional and neuroscience-based techniques.

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (Moher et al.) to select research papers that provide new insight into the role of neuroeconomics in the advertisement industry. The methodology is explained with five sections: search strategy, inclusion and exclusion criteria, databases, and study selection.

### *Search strategy*

The databases used for searching were PubMed, JSTOR, DOAJ, and Nature Communications. The keywords used in searching were generated through the reading of definitions related to the research question in academia. The relevant papers found from each of the databases used the following keywords applied to the title and abstract: "neuromarketing", "neuroeconomics", "advertisement", "decision-making", and "marketing". A combination of keywords was most often used including: "neuromarketing in advertisement" or "neuromarketing and decision-making" as two examples.

### *Inclusion and exclusion criteria*

The target of this systematic review is healthy adult populations with no dementia and full cognitive ability that have data via neuroscience to gauge the advertisement industry. The selected studies applied neuromarketing methods in advertising campaigns and used such techniques to determine neural correlates of both cognitive and emotional processes. Study outcomes included findings on relationships between regions of the brain in response to advertisements, brain activity signaling neural correlation to the processes mentioned earlier, the differences between traditional methods and neuromarketing and its impact, and the benefits behind adopting neuromarketing techniques for product advertisements. The study design is experimental studies, more specifically, pre-test post-test control group design.

### *Databases*

The databases listed were searched from the earliest available date to August 7, 2021: PubMed (from 1966), JSTOR (from 1665), DOAJ (from 2002), and Nature Communications (from 2010). The reference section was analyzed to find more articles in the full papers included in the review. All papers were stored in Zotero version 5, and duplicates were deleted.

### *Study selection*

The screening was done on Zotero, and one person was involved in the process and completed the screening. Articles were stored in Zotero, a reference managing software, where duplicates were deleted. Titles were screened for relevance, category, and language, and those that did not satisfy the criteria were deleted. The abstracts of the remaining papers were then screened in further detail.

### **Results**

Two hundred one records were identified through database searching. Duplicates were removed (n = 64) and one hundred thirty-seven abstracts were screened. Sixty-six abstracts were assessed

for eligibility and twenty-four studies in full text were analyzed further. Figure 1 is the PRISMA flow chart of the process of screening and determining eligibility and inclusion in the review.

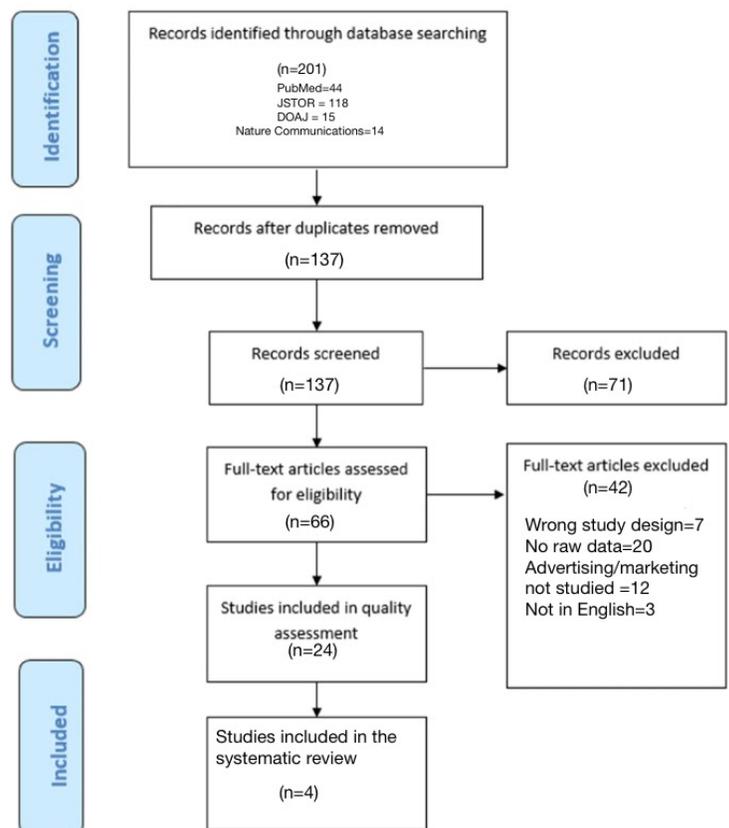


FIGURE 1: PRISMA flow diagram of the process of screening and determining inclusion in the review.

### *Techniques used in studies*

As previously mentioned, neuromarketing is so highly sought after because of its use in determining the advertisement's effect on the consumer in projecting how well the product would do. The techniques discussed in the selected studies were EEG, fMRI, biometrics, and eye-tracking. These techniques were compared in a study based on the core measures of advertising research: attention, affect, memory, and desirability, extended from the AIDA model (Venkatraman, 2015). First, details of each measure will be discussed, then how traditional measures are insufficient, the specifics of each non-traditional technique, and finally a summary

of multiple results on which technique was the best to use in predicting ad success and elasticity will be presented.

### *Core measures in advertising research*

#### *Attention*

Attention, generically, is the level of alertness or ability to interact with the environment (Lindsay, 2020). However, in terms of neuroeconomics, it is the ability to capture the focus of the consumer through informativeness, relevance, etc. Thus, attention can be divided into endogenous and exogenous attention. Endogenous attention is cognitive in origin and allow the consumer to control where their attention lies. It is sometimes also called “top-down” attention. Exogenous attention is the opposite, which describes how “salient” (prominent or noticeable) a stimulus is regarding its characteristics (Erickson, et al., 2015). Exogenous attention can additionally be referred to as “bottom-up” attention. With only traditional methods, distinguishing between these types of attention is not possible.

#### *Affect*

Affect as defined by the circumplex model, arises from two independent neurophysiological systems with one related to valence and the other related to arousal. Valence is the feeling of pleasantness or unpleasantness while arousal is the physiologic activation or deactivation, also known as alertness. (Posner, et al., 2008). When using traditional methods to measure affect, it would be inaccurate due to distortion from high-level cognitive processes.

#### *Memory*

Memory is another core measure and is associated with the three processes of encoding, consolidation, and retrieval. Advertisement research focuses on retrieval which itself has two measures: recall and recognition.

#### *Desirability*

Desirability is how much the people want the product in the ad, measured by contrasting

purchase intent before watching the ad and after. Desirability may be biased through increased desirability for more popular luxury brands if measured using traditional methods.

#### *Traditional methods used in advertising*

As mentioned in the introduction, some common traditional methods include self-reported measures like surveys. This section aims to go more in-depth into the traditional methods in order to properly compare it to modern neuromarketing techniques. Traditional methods include interviews, focus groups, surveys, and questionnaires. In interviews, the results are purely qualitative, as results are based only on what the customer says or how they respond. Contrary to this, surveys and focus groups provide both qualitative and quantitative results because of the different structure of questions asked as well as how the research is conducted. In surveys, participants are given questions that are either in a closed format (i.e., multiple choice or multi-select) or in a short response. Focus groups are similar to interviews but have multiple participants actively answering instead of just one. Finally, questionnaires are similar to surveys, but all of the questions are in a closed format with pre-determined answers, therefore providing only quantitative results (Straker et. al., 2013). All of these methods are commonly used to explore the how, what, and where, less so the why in the relationship between the customer and the marketed product (Zaltman, 2003).

#### *Neuromarketing techniques' use in evaluating core measures of research*

In the previous paragraphs, the referred techniques were EEG, fMRI, biometrics, and eye-tracking. In this section, the mechanics of each technique and which measures they analyze will be mentioned.

#### *Eye Tracking*

Eye tracking, as the name suggests, tracks the movement of your eyes and analyzes it. It's used to determine the relationship between visual

attention and arousal (affect), and the responses of consumers (Oliveira Joaquim dos Santos et al., 2015). Eye-tracking measures three main variables, the gaze point of the eye (what the consumer is looking at), eye movement compared to the position of the head, and pupil dilation (Zurawicki, 2010). Through these variables, eye tracking may be able to determine where the attention is directed at through examining the gaze point as well as to measure arousal through pupil dilation (Duchowski, 2003). The reason eye tracking is used in neuroeconomics is that eye movements are closely related to high-order cognitive processes and because vision is one of the main modalities of receiving stimuli.

### *Biometrics*

Biometrics measure the physiological and automatic responses to external stimuli. The variables measured with biometrics are most commonly heart rate and galvanic skin response (or skin conductance) (Cherubino et al., 2019). Several studies have found that heart rate is related to the valence (affect) of stimuli, the positive or negative feeling. It was hypothesized that an index of attention could be heart-rate deceleration through parasympathetic response, which occurs in information processing (Graham & Clifton, 1966; Baldaro et al., 2001) Galvanic skin response, quantified through skin conductance level (SCL) and short-duration skin conductance responses (SCRs) are considered to be a good measure of changes in arousal caused by sympathetic activation (Critchley, 2002).

### *EEG*

EEG uses electrodes applied to the scalp or a head cap which measure the voltage of action potentials and the frequency of oscillations (measured in Hz) determining brain activity. EEG consists of 5 frequency bands of delta, theta, alpha, beta, and gamma, listed in increasing frequencies. Data from EEGs include spatial and temporal low amplitude signals which are separated into multiple components (each

frequency band) through a power spectrum analysis. In consumer neuroscience, many studies using EEG will try to estimate cortical activity and reconstruct the 3D configuration to identify specific brain areas involved (Bazzani et al., 2017). The specific brain areas that are analyzed (regions of interest, or ROIs) are orbitofrontal, prefrontal, anterior cingulate cortex (ACC), cingulate motor (CMA), parietal, and occipital alpha areas as well as measures of frontal asymmetry. These areas are associated with the measures of attention (occipital alpha, ACC, CMA), memory (parietal, prefrontal), and affect (a measure of frontal asymmetry).

### *fMRI*

fMRI combines magnetic fields with radio waves allowing the viewing of brain structures. In experiments the subject is placed on a bed with their head surrounded by a magnet allowing protons inside their head to align with the magnetic field and active parts of the brain will have more blood flow, less oxygen-free hemoglobin, producing a BOLD (Blood Oxygen Level Dependent) signal that can be viewed on a computer. (Zurawicki, 2010). This process allows for observation of intricate brain structures, localizing brain activity changes even deep within the brain (Plassmann et al., 2008). fMRI also analyzes specific ROIs including the dorsolateral prefrontal cortex (dlPFC), ventral striatum, ventromedial prefrontal cortex (vmPFC), amygdala, and hippocampus. These regions are associated with measures of attention (dlPFC, vmPFC), affect (amygdala), memory (hippocampus), and desirability (vmPFC, ventral striatum). Table 1 lists each technique, and which measures they are associated with.

In the 2015 study done by Venkatraman et al., the techniques were examined to test for correlations between ad-related and product-related measures. Ad-related measures included liking, familiarity, relevance, informativeness, and responsiveness. Product-related measures included changes in purchase intent, usage

**TABLE 1:** Neuromarketing techniques and the associated core measures

<b>Techniques</b>	<b>Core Measures</b>			
	<i>Attention</i>	<i>Affect</i>	<i>Memory</i>	<i>Desirability</i>
<b>Eye Tracking</b>				
Pupil size		+		
Fixation count	+			
<b>Biometrics</b>				
Heart rate deceleration	+			
Skin conductance		+		
<b>EEG</b>				
Occipital alpha	+			
Frontal asymmetry		+		
Parietal area			+	
Prefrontal area			+	
Anterior cingulate cortex	+			
Cingulate motor area	+			
<b>fMRI</b>				
Dorsolateral prefrontal cortex	+			
Ventral striatum				+
Ventromedial prefrontal cortex	+			+
Amygdala		+		
Hippocampus			+	
Anterior cingulate cortex	+			

intent, recommendation intent, familiarity, and recognition. In this section, the correlations found for each technique will be discussed, first for Venkatraman's study and then for other related studies.

*Eye Tracking and Biometrics*

In the analysis of eye-tracking, the percentage of fixations on a certain part of the commercial correlated with the measure of liking, consistent with findings that liked ads were associated with

increased attention. In the analysis of biometrics, deceleration of heart rate correlated with liking, recognition, and change in purchase intent, increasing the possibility of purchasing the object/service advertised. (Venkatraman et al., 2015)

*fMRI*

In the analysis of fMRI, activations in the right amygdala, dlPFC, and vmPFC were associated with liking. Activations in the vmPFC and ACC

were associated with increased purchase intent. Activations in the hippocampus, as hypothesized, were associated with recognition. (Venkatraman et al., 2015) The technique of fMRI was also used in the 2017 study by Vezich et al. which found that an engagement of the vmPFC and ventral striatum influenced purchase intent. Additionally, the 2015 study by McFadden et al., used fMRI too, with application to egg production systems where the subjects were presented with multi-attribute choices with conflicting individual attributes (i.e., increased price for cage-free eggs) to test activation in dlPFC. The study found that the right dlPFC (rdlPFC) signaled a larger response to information. However, the study didn't find this with the left dlPFC (ldlPFC), suggesting a laterality effect. Not only did the activation of rdlPFC increase the responsiveness to the ad, but activation also implied that the participants thought about the tradeoff in the multi-attribute choices. Furthermore, people with more uncertainty (i.e., people who don't feel particularly strong about one side or the other) were more responsive.

### *EEG*

In the analysis of EEG, ads with higher arousal levels were associated with higher frontal asymmetry (Venkatraman et al., 2015). The technique of EEG was also used in the 2008 study by Astolfi et al., finding that cortical activity during the observation of ads that were forgotten is different from the activity during those that were remembered. They also found that the prefrontal and parietal areas were critical in recognition through storing and remembering information. Those areas had a high increase in cortical connectivity inflow. Moreover, the ACC and CMA were found to increase attention, thus liking because of the increased outflow out of those areas. All observations were found across all frequencies, so they were not frequency dependent.

Table 2 lists all of the techniques and the correlations they were discovered to have with both ad-related and product-related measures. Comparison between the effectiveness of techniques applied to real-world ads and companies

After examining the cognitive processes leading to increases in the related measures, research of the effectiveness of each technique when applied to real-world scenarios was done to discover which technique was the most useful. The 2015 study by Venkatraman et al. investigated which technique best explained the variation in advertising elasticities. Advertising elasticity of demand (ad elasticity) measures a company's advertising campaign's effectiveness in producing new sales. Needless to say, anything that is a good predictor of ad elasticity would be greatly beneficial to a company, as they would be able to visualize how well the product would do. The study found that only fMRI measures were significant predictors of ad elasticities, more specifically, the positive impact of activation in the ventral striatum. Eye-tracking and EEG measures were moderate predictors, but not as significant as those of fMRI.

### **Discussion**

#### *Weaknesses of traditional methods*

In the attempt to compare and contrast traditional methods with neuromarketing ones, the flaws of traditional methods must be identified. The methods of surveys and questionnaires often rely on customer awareness and self-reflection as they have to recall a previous experience with the advertised product/service and thus are categorized as "reactive" or "backwards looking". Often times that memory will be biased as the "conscious mind finds it almost impossible to resist putting its spin on events." This is known as recall bias (Graves, 2010). Focus groups and interviews also have weaknesses because they cannot build the trust to discuss personal feelings over the short speaking time of ten to twelve minutes. The data collected are harder to analyze

**TABLE 2:** Neuromarketing techniques and their respective correlations with ad-related and product-related measures

Techniques	Ad-Related Measures		Product-Related Measures	
	Liking	Responsiveness	Purchase Intent	Recognition
<b>Eye-Tracking</b>				
Fixation count	+			
<b>Biometrics</b>				
Heart rate deceleration	+		+	+
<b>EEG</b>				
Frontal asymmetry		+		
Prefrontal areas				+
Parietal areas				+
Anterior cingulate cortex	+			
Cingulate motor area	+			
<b>fMRI</b>				
Dorsolateral prefrontal cortex	+	+		
Ventromedial prefrontal cortex	+		+	
Amygdala	+			
Anterior cingulate cortex			+	
Hippocampus				+
Ventral striatum			+	

than the surveys and questionnaires which have pre-determined answers. Furthermore, in traditional methods, the participants may not be able to evaluate their decisions and priorities with one potential cause being that they feel the need to provide a socially “acceptable” response.

*Strengths of neuromarketing techniques*

A study done in 2020 by Nilashi et al. examined the factors that impacted advertising managers’ decision in choosing to use neuroscience techniques specifically for sustainable product marketing (green marketing). They found that the

benefits of neuroimaging for neuromarketing are based on a few assumptions. The first is that the brain of consumers contains invisible information regarding their motives and if discovered, could increase product design and enhance sales. The second is that neuroimaging information would be a more precise indicator of priorities compared to information obtained from traditional methods and would be insensitive to bias. The benefits of neuroimaging include simultaneous tracking of the consumer’s neural response during processing of desired stimuli, therefore eliminating the recall bias mentioned before. It can

also capture the thoughts, emotions, and state of mind that happens below the level of awareness of the consumer (Stanfey et al., 2003). Also mentioned before, these cannot be measured by traditional methods. Nilashi et al. also found that accuracy and bias were the two factors that had a significant influence on marketers in utilizing neuromarketing for advertising and branding purposes.

Similar to this “application” or real-world driven comparison, the study findings mentioned in the results section suggest that neurophysiological methods can explain the relationships among regions of the brain and the resulting cognitive processes as well as variance in ad elasticities much better than traditional ad methods. Those relationships provide insight into the increase or decrease of each core measure via comparison to the regions' neurological roles. Because it can visualize the relationships between areas of the brain so well, the best predictor of ad elasticities is fMRI, which is also able to accurately evaluate the most amount of core measures.

#### *Implications and limitations of the study*

Future research could be on how advertising campaigns could alter their ads to target people with more uncertainty, thereby increasing responsiveness, or in general, altering their ads by making little changes using the given knowledge to see which would impact consumers the most. Other future implications would be an uprising in the use of fMRI techniques in neuromarketing, and an investigation of which core measure plays the largest role in ad elasticity.

This study includes several limitations. First of all, the number of studies subject to analysis was low, so, arguably, any conclusions drawn are not reliable. Secondly, the number of studies available is questionable because of the many databases that were behind a paywall. Finally, as one person, the reviewing of all the articles in every database was not possible and an in-depth analysis of the

sheer number of articles on this topic over the past decades was not feasible.

## Conclusions

This review screened over 200 papers to determine the role of neuroeconomics in the advertisement industry. The techniques used in neuroeconomics, the relationships they found, and which one was best for predicting advertisement success were criteria that were all addressed. However, it is important to remember that there was a low number of studies analyzed here and the results may be more significant if a higher number were used.

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# Perception of Sexuality and Gender Identity in Anime: How Positive Representations Could Be Used to Combat LGBTQ+ Discrimination

Xuetao Wu

Belmont High School, United States  
xwu2023@gmail.com

## Abstract

People within the LGBTQ+ communities are often stigmatized and rejected. Most occurrences of LGBTQ discrimination are actually microaggressions or ostracism that is performed subconsciously due to our inherent bias. One possible way to address the adverse effects of unconscious bias is by introducing entertainment into the lives of children and adolescents through a hidden curriculum designed to normalize LGBTQ+. Hidden curriculum has shown to have a direct influence on a person's ideology and behavior. This research paper will focus on how the hidden curriculum found within Japanese animation or anime can combat discrimination against LGBTQ+ communities. Animes were selected utilizing criteria set within the article, and 4 were chosen for in-depth analysis. Specifically, the author reviewed examples of internalized homophobia and interpersonal discrimination, and prejudice found in these animes. It is discovered that promoting animes (or any type of media) with a positive representation of LGBTQ+ could diminish a person's bias and prejudice to an extent. Therefore it is crucial to use television shows and movies (anime or not) as pivotal educational tools in promoting equality.

*Keywords: Anime, LGBTQ+ discrimination, hidden curriculum, effects of media*

## Introduction

People within the LGBTQ+ communities are often the minorities, forming enclaves to resist discrimination and avoid people, stigmatization, and rejection due to their sexual orientation or gender identity (Brown, 2007; Green, 2008). The Human Rights Campaign defines sexual orientation as "an inherent or immutable enduring emotional, romantic or sexual attraction to other people." Gender identity is described as "one's innermost concept of self as male, female, a blend of both or neither – how individuals perceive themselves and what they call themselves." Although advancements have been made to prevent prejudice due to sexual orientation - such as the Supreme Court case, Obergefell v. Hodges, which legalized same-sex marriages - people within the LGBTQ+ community often face harassment from local law enforcement, which often impedes the efforts of national actions for equality (Kazyak and Stange, 2018; Mallory et al., 2015). Across all countries, there is a historical and contemporary trend where a change in the social environment has resulted from increased rights and visibility for the LGBTQ+ group on the national level, yet frequent local community discrimination is still quite evident (Kite and Bryant-Lee, 2016). As seen in China, where the government removed homosexuality and bisexuality as a category from the Chinese Classification of Mental Disorders 3 (CCMD-3) in 2,000, but many mental health professionals

continue to hold the belief that homosexuality is just another mental health disease, similar to depression, that can be cured through "conversion therapy" (Wang et al., 2019; Cen, 2017).

Continued intolerance and marginalization caused by our homophobic society have continued to take people's lives and opportunities in the LGBTQ group. Just 4 years ago, in June of 2016, a massacre at Pulse NightClub claimed the life of over 50 people, many of whom were murdered for identifying as part of the LGBTQ group (Durso, 2017). Most occurrences of LGBTQ discrimination are actually microaggressions or ostracism that is performed subconsciously due to our inherent bias in which no amount of federal laws could diminish (DeSouza and Wesselmann, 2017; Frith, 2015). Bias is part of our identity shaped by the culture, people, and situation that person surrounds himself with, contributing to a person's daily social perception and behavior (Greenwald and Lai, 2020). One possible way to address the adverse effects of unconscious bias is by introducing entertainment into the lives of children and adolescents through a hidden curriculum designed to normalize LGBTQ+.

This tactic has been used before to achieve similar outcomes. For example, an attempt to combine entertainment and education to educate and influence young adults on sexually transmitted diseases achieved great success (Glik et al., 2010). Entertainment could also be used to subconsciously shift the behavior and attitude of an individual through prolonged contact. Data from 98 independent studies show that playing violent video games resulted in a positive correlation of increased aggression that affects the participants both short and long term (Greitemeyer and Mugge, 2014). A few available studies have found that mainstream mass media directly affect our perception of our sexuality and influences our behavior (Brown, 2010).

This paper will focus on how the hidden curriculum found within Japanese animation or anime can combat discrimination against LGBTQ+ communities. Anime was chosen as the type of media contended due to its wide following across the globe, as shown by its market value of around 23.56 billion USD (not counting the visual novel, anime-related games, and manga) (Grand View Research, 2021). A systemic analysis was conducted to determine how anime could normalize the LGBTQ+ community in parts of our society that is homophobic.

### Methodology

This study uses a mixed-method systematic review to support the thesis for this paper.

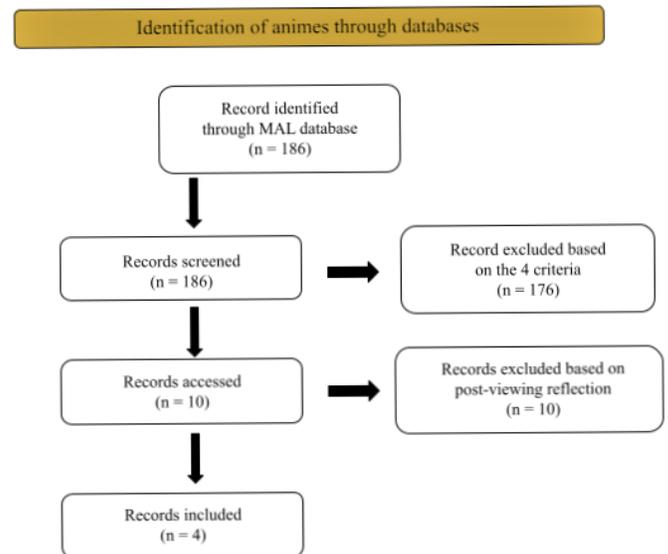


FIGURE 1: Depicts the process of selection for animes used in this study.

Animes were selected utilizing the genres shounen-ai (boy's love) and shoujo-ai (girl's love) onto an online database for anime titles called My Anime List for review (Figure 1). Initially, there were 186 shows under the category of Shounen-ai and Shoujo-ai.

These shows were then screened based on the 4 criteria listed below.

- The show's relevancy on the topic of LGBTQ+. More specifically, getting rid of the shows that feature an LGBTQ+ character as a running gag to fit into a comedic stereotype or characters irrelevant to the main plot.
- The quality of the show is based on public ranking given out in My Anime List and Anime-Planet.
- The relatability of these shows compared to average teenagers/high school student's daily life. Although supernatural/sci-fi-themed shows were included in this study, flat-out fantasy shows were not due to the preposterous events happening within the show.

After comparing the synopsis, reviews, and online recommendations of these anime to the criteria listed above, these 9 shows and 1 movie were chosen for further screening.

- Anime Shows
  - Hourou Musuko (2011)
  - Aoi Hana (2009)
  - Mikagura Gakuen Kumikyoku (2015)
  - Neon Genesis Evangelion (1995)
  - Yuri!!! on Ice (2016)
  - No 6 (2011)
  - Citrus (2018)
  - Lupin III (1971)
  - Cowboy Bebop (1998)
- Anime Movies
  - Doukyuusei (2016)

The shows were viewed in their entirety. 4 questions were considered following each viewing session to check for eligibility.

- Question 1: Was this anime a positive representation of the LGBTQ+ community?
- Question 2: Did I develop a new understanding regarding the unique

experiences of people who identify as LGBTQ+ due to behavioral, emotional, and cognitive differences?

- Question 3: Did I develop a new perspective of the LGBTQ communities as a whole?
- Question 4: If I witness a similar situation in real life, would I be more likely to perceive the situation as normal?

Lupin III, Mikagura Gakuen Kumikyoku, Cowboy Bebop, Neon Genesis Evangelion, No 6, and Doukyuusei were excluded in the paper due to insufficient LGBTQ+ content found within the show. The final 4 shows that are included in this paper are (See Appendix A for more information about the following animes) :

- Hourou Musuko (2011)
- Aoi Hana (2009)
- Yuri!!! on Ice (2016)
- Citrus (2018)

Post viewing of the anime, overlapping themes are analyzed with the content of the show itself.

A secondary systematic review was also done to support the thesis (Figure 2). A broad range of search terms was used across databases Pubmed, Google Scholar, and JSTOR (See Appendix B for search terms). After compiling all the search results, duplicates and articles unavailable to the author were excluded. In this stage of evaluation, articles were examined based on their title or abstract. Two ideas are presented within this paper, the effects of hidden curriculum and media and injustices experienced by members of the LGBTQ+ community; if the article doesn't specifically have a section that dealt with these two points, it was excluded. 335 articles were screened based on title or abstract. A final of 122 articles was thoroughly examined utilizing the complete text, and 41 articles were included in the final review due to relevancy or redundancy. An additional 7 articles were found through hand searching methods.

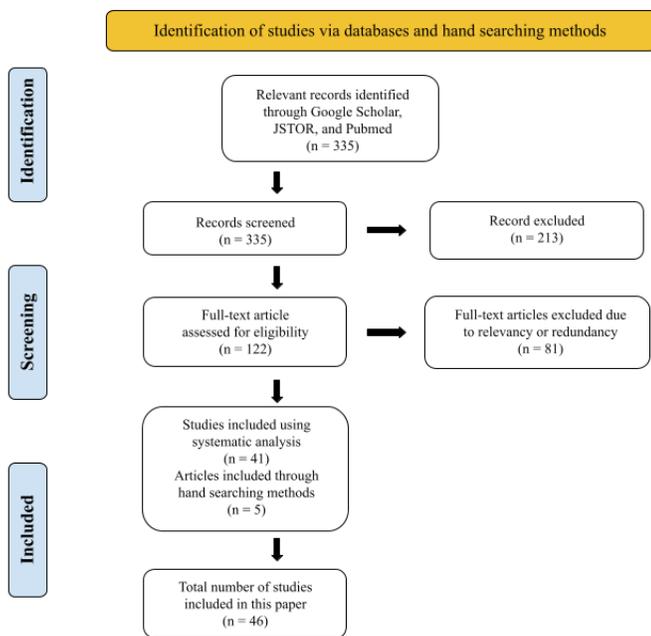


FIGURE 2: PRISMA flow diagram depicting the systematic review of 335 articles evaluated in this study.

## Results

A person's development of his own moral value, ethics, and perception of what's right or wrong includes all pedagogical, cultural, and social factors they surround themselves with (Bornstein, 2017; Berry, 2005; Lickona, 2006). This process is also responsible for a person's character and behavior (Zuhai, 2012). A person's character also measures their willingness to maintain a respectful attitude and conscious decision to not discriminate against people with differing viewpoints in sexuality and gender identity (Battistich, 2005; Dodd, 1991). In our past, media that told stories of LGBTQ+ characters are often queer-coded - a character whose sexuality is not confirmed but is coded as a queer through stereotypes and exaggerated traits and characteristics (Fisher et al., 2007; Pullen, 2016). Due to our homophobic culture, coded characters are often shown as depressed, desperate, or perverse (Kim, 2017). Due to the way media often changes our social cognition, dictating how we should feel about ourselves or others, queer-coded characters that spread negative (often

false) information about the LGBTQ+ community is dangerous, to say the least (Firth, 2019). This was one of the causes of hostility towards LGBTQ+ groups that are experienced frequently, with 51% are reported to have been called slurs, 53% experienced microaggression, and 51% experienced some forms of violence (Casey et al., 2019). This data exemplifies the importance of a more positive representation of the LGBTQ+ community in media. The paper will now be listing the overlapping themes between the 4 anime reviewed to break down the positive expression found within them. It is also important to note that these anime were not selected randomly but based on how well they represented their LGBTQ+ characters in a more developed and realistic manner.

### *Internalized Homophobia*

The internalization of homophobia exists due to LGBTQ people living within a heteronormative society and developed a need to compensate for their lack of normalcy through self-loathing, self-abuse, and a more extreme emotional state (Thepsourinthone et al., 2020). Internalized homophobia is a significant cause of mental distress that results in self-harm or suicide (Shidlo, 2013). A study at LA Trobe University found that 42% of gay participants indulged in weekly alcohol consumption to escape reality (Hillier, 2010). The fears of being excluded from their preferred social groups often cause many gays to reject their sexual orientation and act in a way that goes against their wishes.

A similar issue is visible in Hourou Musuko. Hourou Musuko tells the story of Shuuichi, who was assigned male at birth but wishes to be a girl, and Yoshino, who was assigned female at birth but wishes to be a boy. At the show's beginning, both characters acted as their birth gender to the best of their ability even though they were in constant dysphoria. At most, they would hint at their hobby of crossdressing without ever finding the courage to admit to the people around them

of the gender they would like to be identified as due to fears of being isolated. The characters also show signs of anxiety about one's own sexual orientation. Being mistaken by the community around them, the two main characters had a misbelief that their sexuality was simply a phase in which they can "grow out of. This fear led them to give up their love interests because they believed their relationship could not be permanent. Within the show, some side characters often support their sexuality, but their self-suppression and thought-policing made them unable to come out. A similar issue is visible in Aoi Hana. Aoi Hana tells a simplistic story surrounding two childhood friends Fumi and Akira separated when they were young before reuniting in high school. The two share a mutual love with one another, however, not as a love interest but under the context of friends. Although they show signs advancing their bond, they are unsure if it's possible to even sustain a same-sex relationship. When Fumi got into a homosexual relationship with an upperclassman, she was ecstatic at first before finally breaking down and clamoring to her friend, "Please don't hate me. Don't think I'm disgusting." Similarly, in the real world, LGBTQ+ members are more likely to have increased social anxiety over other's perceptions and a greater need to achieve gender conformity than people who are heterosexual (Skidmore et al., 2006; Pachinkis and Goldfriend, 2006). The story continues to develop as both characters struggle to find their sexuality and learn how to speak up about how they truly feel. Coming out as part of the LGBTQ+ community is not as static as western media perceives it to be. It is a long struggle of self-discovery and overcoming society, stigma, and yourself (Rosenburg, 2017).

In Yuri on Ice, the internalized homophobia was not about self-hatred or self-discovery but focuses more on finding the courage to express oneself beyond the gender traditional gender norms. It tells the story of Yuuri, an inspiring figure skater who is depressed due to his string of losses, and

Victor, who is a 5-time world champion, determined to train Yuuri to help him win the next Championship. In the world of figure skating, it is generally frowned upon by the judges, tv audience, and sponsors alike for male skaters to adopt a more feminine style. This story tells its tale through its animation. As Yuri gets better at figure skating, he discovers that being more feminine with his movement suited him better than a masculine role. He begins to perfect this more eloquent movement style to express his love for Victor, his coach. This story examines the hardship of portraying your sexuality to the public.

#### *Interpersonal discrimination and prejudice*

Humans naturally respond emotionally to interpersonal discrimination and prejudice, including anger, jealousy, loneliness, shame, guilt, social anxiety, and embarrassment (Leary, 2015). People strive for social acceptance and belonging, and being faced with discrimination, ostracism, and stigmatization might cause someone to be anti-social and socially avoidant (Richmond and Leary, 2009). These forms of discrimination often come in the form of unintentional derogatory messages known as microaggression (Nedal et al., 2016). Regardless of age, income, education, and self-rated health, any person experiences some psychological distress from any level of discrimination (Ajrouch, 2010). Social distress shares similar psychological responses as physical pain; thus, we must understand the consequences of unconscious microaggressions on people with different sexuality and gender identity (Rita et al., 2016).

In Hourou Musuko, when Shuuichi wants to try on her sister's dress, her sister catches her in the act and calls it disgusting. This lowered Shuuichi's self-esteem and caused him to wander off from home to seek comfort. This scene demonstrated the vulnerability of individuals with nonconforming sexuality. A study showed that those who disclosed their sexual orientation to family members often received more verbal and physical

abuse and quickly became more suicidal as a result (Augelli, 1998; Katz-Wise et al., 2017). Another example was when Shuuichi was teased for writing in her journal, "Juliet, why are you a girl? Why am I a boy," referencing the Romeo and Juliet story. In this scene, she expresses her discontent with her gender but cannot do anything about it. The people around Shuuichi continue to repudiate his identified gender daily in small-scaled microaggression. Although each act doesn't seem to be too prevalent, constant getting berated for your own sexuality in the forms of microaggression and victimization would eventually lead to stress on the body and mind (Haines et al., 2017; Nadal, 2018). Victims are often left more doubtful of themselves and worries excessively about their sexuality (Seelman, 2016).

Another pivotal example can be found in Aoi Hana. Aoi Hana depicts a world similar to ours in which the heteronormative code is slowly becoming less prevalent, but unconscious discriminatory actions are still very much a thing. The people at their high school have a gossip culture in which groups love to discuss who is homosexual and who is dating who. Although gossiping is seen as a frequent social activity, it inspires fear in someone who is actually homosexual. Our main character Fumi was afraid to become the topic of the gossip; as a result, she struggles to maintain her identity as a lesbian. She chooses to actively hold back her "gay" feelings onto many women that she wanted to date.

The anime, Citrus, is also a great example of this occurrence. Citrus is about the development of their relationship with two girls (Mei and Yuzu) as they try to understand the confusion of the feelings of their romantic person towards one another. After they have started dating, Yuzu constantly runs back home crying due to the homophobic threats in school. Sexual minorities are often the target for bullying and cyberbullying in school (Abreu and Kenny, 2018). Such discrimination resulted in 28% of the reported

homosexual teenagers having suicidal ideation (Bouris et al., 2016). Other studies have shown that teenagers experienced a higher chance of mental health problems, high school drop-out, substance abuse, and troubles with the law (Remafedi, 1987; Lock, 1998).

### **Discussions**

The study revealed some of the LGBTQ+ representation found within anime that mainstream media has not yet explored. Many research papers focus on how media misrepresents or underrepresents the LGBTQ+ community while ignoring that some shows help combat the stereotype or biases by having a more realistic and empathetic representation of LGBTQ+. Hidden curriculum is a concept that explains how culture, structures, and institutions influence a person's cognitive behavior (Athina, 2015). It is not just a simple transmission of information but a process of socialization in which morals, norms, values, and beliefs are subconsciously conveyed to the viewer (Mahood, 2011). This means that promoting animes with a positive representation of LGBTQ+ could diminish a person's bias and prejudice to an extent. For example, people could watch the anime, Hourou Musuko, to understand the thoughts and feelings of people who consider themselves transgender. They get an opportunity to empathize with the characters and get the chance to feel emotionally distraught when these characters get discriminated against. The viewers can develop an emotional bond with these fictional characters because we can witness their growth. This will result in a greater understanding of people with different sexuality or gender identities, reducing bias.

There is imputable evidence that media influences people, both emotionally and socially (Anderson and Bushman, 2003). Life in modern times depends on the media that is both invasive and persuasive; thus, it has become the key to communicating good social values (Deuze, 2011). The media has played a fundamental role

in the world's relationship with transphobia and homophobia, both in the historical disparaging remarks about the LGBTQ+ community as well as the current Gay Pride Movement (Hubbard and Hegarty, 2014). Due to the effects of media, well-thought-out shows portraying LGBTQ+ couples satisfied with their lives are an essential representation of the LGBTQ+ community. It is crucial to use television shows and movies (anime or not) as pivotal educational tools in promoting equality.

## Conclusions and Limitations

The animes chosen to be used in the analysis put a lot of emphasis on finding LGBTQ+ characters that go beyond filling a character trope or his sexuality in a comedic effect intended to make light of the social stigma at hand. It is important to note that there are many subtle LGBTQ+ characters found in anime in which the shows never commit to articulating their romance - only same-sex crushes portrayed in a very unrealistic and fetishized manner. Even characters popular within the homosexual romance genre are not good representations of the LGBTQ+ community due to the moe love presented historically in Japan (Galbraith, 2009). Because no research was done surrounding the negative representations found in anime, it is hard to make a decisive conclusion on the effects of anime and how it could influence a person's belief and behavior. More studies with greater sample size and participants from a broader range of backgrounds need to be conducted to determine the effectiveness of this strategy to combat LGBTQ+ discrimination. Future studies could also include the roles of cultural knowledge and ethnicities in their perception of these pro-LGBTQ+ animes. This paper only aims to introduce the possibility of how we approach the problem of LGBTQ+ discrimination; by shifting away from some focus from fighting for civil rights in Congress, courtrooms, or out in the streets (although this is equally important) to a more subtle approach of normalizing the LGBTQ+

communities in the beliefs of young adults through the use of hidden curriculum found within anime or any type of media.

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## Appendix A: Information regarding the selected anime.

- Hourou Musuko (2011)
  - Studio: AIC CLASSIC
  - Director: Ei Aoki
  - Genres: Drama, Romance, School, Seinen, Slice of Life
- Aoi Hana (2009)
  - Studio: J.C. Staff
  - Director: Ken'ichi Kasai
  - Genres: Romance, Shoujo Ai, Slice of Life
- Yuri!!! on Ice (2016)
  - Studio: MAPPPA
  - Director: Sayo Yamamoto
  - Genres: Comedy, Sports
- Concept 2: Effects of media and its hidden curriculum
  - Hidden curriculum, character, behaviors, positive representation, bias, social values, and media

- Citrus (2018)
  - Studio: Passione
  - Director: Takeo Takahashi Naoyuki Tatsuwa
  - Genres: Drama, Romance, School, Shoujo Ai

## Appendix B: Search terms

- Concept 1: Discrimination among LGBTQ+
  - Sexuality, gender identity, discrimination, LGBTQ+, microaggression, systematic prejudice, queer-coding, unconscious bias, ostracism, homophobia, and transphobia

# NIH Research Funding for Palliative Care and COVID-19

Jonathan Wun<sup>1</sup>, Laura P. Gelfman, MD, MPH  
<sup>1</sup>Stuyvesant High School, United States  
jonwun123@gmail.com

## Abstract

The COVID-19 pandemic has created a multitude of hardships, especially concerning the treatment of patients within overwhelmed hospitals. It is in this environment that palliative care has played an important role: providing care for isolated patients and exhausted physicians, communicating with patients' families, and making serious decisions. This report serves to examine the impact of COVID-19 on federally funded COVID-19 related palliative care research and grants. The term "COVID-19" was inputted into the NIH RePORTER along with the terms: "palliative care," "end-of-life-care," "hospice," and "end of life" generating 81 unique grants. After hand reviewing these grants, 17 were identified to be pertinent to COVID-19 and palliative care. These grants investigated research topics such as systems of care, physical symptom management, and decision making/communication, which align with key elements essential to the delivery of high-quality bedside palliative care during a pandemic. The results of this study are similar to the 2011–2015 analysis of palliative medicine NIH funding. The same major funding institutes (NCI, NINR, NIA) were identified and the percentage of COVID-19 palliative care funding relative to the total number of COVID-19 grants remains at less than 1%. Despite the urgency for palliative care throughout hospital systems, palliative care grants continue to constitute an insignificant percentage of the total COVID-19 awards approved by the NIH. Additional initiative is called for to support future palliative care research.

*Keywords: COVID-19, Palliative Care, National Institutes of Health (NIH)*

## Introduction

Originating in Wuhan, China, the SARS-CoV-2 virus has spread around the world since its discovery in late 2019, resulting in the COVID-19 pandemic and the deaths of millions (Umakanthan et al., 2020). By February of 2020, New York City (NYC) became an epicenter of COVID-19 in the United States, with over 200,000 confirmed cases within three months. NYC data between February and June shows that the rate of hospitalization and death is greatest for people aged  $\geq 75$ , with a 38.3% mortality rate in this age group (Thompson, 2020). Nationally, the CDC has found that adults of 75–84 years old have nine times the rate of hospitalization and 230 times the rate of death as compared to that of those in the 18–29-year-old age group (CDC, 2021). Hospitalized older adults often experience severe symptoms (dyspnea, high respiration rate, hypoxemia and delirium) and/or critical illness (respiratory failure, septic shock) (Umakanthan et al., 2020; Fadul et al., 2021). Given the soaring mortality rate, the high symptom burden, and the social isolation put in place to decrease further spread of COVID 19, palliative care has become an essential part of the COVID-19 management of hospitalized patients (Blinderman et al., 2021; Fadul et al., 2021; "Palliative care", 2020).

Palliative care is an interdisciplinary team approach focused on the management of physical symptoms, pain, and emotional health, in addition to communication and advanced care planning

(ACP). The primary goal of palliative medicine is improved quality of life for not only the patient, but also for family members (NCHPC, 2018; WHO, 2020; CAPC, n.d.). Throughout the COVID-19 pandemic, palliative care has been utilized to deal with hardships, from patient isolation and online family communication to providing staff with psychological support (Fadul et al., 2021; Janssen et al., 2020). Palliative medicine also played a key role in decision making, in addition to maintaining communication with a patient's family given limited visitations (Blinderman et al., 2021). While some patients may choose to extend their life by undergoing intubation, others may value comfort over quantity of life. It is important for providers to explore patient wishes so that treatment plans can be aligned with patient goals (Ting et al. 2020). Hospitals in the northeast overfilled with COVID patients relied on palliative care to meet these patient and family needs (Aaronson et al., 2020). Overstretched palliative care teams explored creative ways to expand the workforce to meet this unprecedented demand. However, it is unclear whether this increase in demand for bedside palliative care correlates with an increase in the funding of evidence based palliative care research, which guides clinical practice and management. This report will examine the impact of COVID-19 on federally funded COVID-19 related palliative care research and grants.

## Methods

NIH grants and supplements relevant to COVID-19 and palliative care were collected by entering selected terms into the NIH RePORTER system. NIH RePORTER is a module that allows for searches of all NIH funded projects, providing corresponding information such as a brief description, the funding institute(s), as well as the primary investigator (HHS, n.d.c). The search term "COVID-19" was entered into RePORTER with each of the terms used to collect palliative care related grants ("palliative care," "end-of-life-care," "hospice," "end of life"). Each search result

was compiled into a collective list of grants, in which duplicates were excluded. Grants funded by federal organizations such as Patient-Centered Outcomes Research Institute (PCORI) and Veterans Administration (VA) were excluded in order to be able to compare this project's results to previous papers.

Both authors (J.W. and L.P.G.) independently categorized the unique grants as to whether or not they were relevant to palliative care based on the definition of palliative care given by the National Consensus Project for Quality Palliative Care (NCP) and the National Coalition for Hospice and Palliative Care (NCHPC). The grants were also separately categorized as relevant to COVID-19, based on whether the terms "COVID" and/or "COVID-19" were explicitly stated within the grant description. This created a uniform way to categorize the grants and to maintain a consistent method of interpretation between the authors. In the case of disagreement, the specific coding of the grant was discussed between the two authors until a consensus was reached.

Each author then categorized grants that were deemed relevant to both palliative care and COVID-19 into one of ten categories: (1) Studies focusing on pain and physical symptom management and quality of life, (2) studies examining psychological, spiritual, and emotional symptoms, (3) Studies of instrument development and measurement, (4) Health services research evaluating systems of care, (5) Decision making and communication studies, (6) Studies of palliative medicine education and training programs, (7) Studies of caregivers and families, (8) Pediatrics studies, (9) Career development awards, (10) Other. Disagreements regarding the primary grant topics were discussed between the two authors until a consensus was reached.

## Results

The initial search of the NIH RePORTER system yielded a total of 151 grant results, of which 81 were unique. Out of these, one grant was

excluded since it was funded by the VA. From the remaining 80 grants, 21 were categorized as

TABLE 1. NIH-Funded Awards For Palliative Care & COVID-19 By Institute, no. (%)

<i>Institute</i>	<i>All Grants</i>	<i>CDA<sup>a</sup></i>	<i>Training Grants<sup>b</sup></i>	<i>Pilot Grants<sup>c</sup></i>	<i>Research Project Grants<sup>d</sup></i>	<i>Education Project Grants<sup>e</sup></i>	<i>Center Grants<sup>f</sup></i>
All Institutes	17	1 (5.9)	1 (5.9)	1 (5.9)	10 (58.8)	–	4 (23.5)
NIA	10 (58.8)	1 (5.9)	–	1 (5.9)	7 (41.2)	–	1 (5.9)
NINR	4 (23.5)	–	1 (5.9)	–	2 (11.8)	–	1 (5.9)
OD	2 (11.8)	–	–	–	1 (5.9)	–	1 (5.9)
NCI	1 (5.9)	–	–	–	–	–	1 (5.9)

<sup>a</sup>CDA (Experienced investigator): K24

<sup>b</sup>Training Grants: F31

<sup>c</sup>Pilot Grants: R33

<sup>d</sup>Research Project Grants: R01

<sup>e</sup>Education Project Grants: n/a

<sup>f</sup>Center Grants: P20, U01, UH3, ZID

The symbol “–” represents there were no funded grants found within that category. CDA, career development award; NIA, National Institute on Aging; NINR, National Institute of Nursing Research; OD, Office of the Director; NCI, National Cancer Institute.

relevant to palliative care and 63 were deemed relevant to COVID-19. Seventeen of the 80 grants were relevant to both palliative care and COVID-19, and the authors agreed that 13 grants did not fall under either category.

### *Types of Grants*

Of the 17 grants that met the stated requirements there were 10 research project grants (R01), 4 center grants (P20, U01, UH3, ZID), 1 career development award (K24, to an experienced investigator), 1 training grant (F31), and 1 pilot grant (R33) (Table 1) (U.S., n.d.a). Some examples of included research project grants include: “The Impact of COVID-19 on End-of-Life Care for Vulnerable Populations”, “Homebound with Dementia in the Context of COVID-19” and “Effects of COVID-19 on Daily Lives of Older Persons with and without ADRD:

National Health and Aging Trends Study Supplement”.

### *Research Topic Area*

Of the 17 grants, 6 (35.3%) focused on health services research evaluating systems of care; 3 (17.6%) funded pain and physical symptom management and quality of life research; 3 (17.6%) addressed decision making and communication studies; 1 (5.9%) funded pediatric studies, 1 (5.9%) supported career development, and 3 (17.6%) funded other palliative care related research (Table 2). No included grants were found within categories not stated.

### *Funding By Institute*

Included grants were found to be funded by four NIH institutes, the National Institute of Aging (NIA), the National Institute of Nursing Research (NINR), the Office of the Director (OD), and the National Cancer Institute (NCI). Ten

grants (58.8%) were funded by the NIA, 4 (23.5%) were funded by the NINR, 2 (11.8%) were funded by the OD, and 1 (5.9%) was funded by the NCI.

TABLE 2. Distribution of Awarded Grants by Research Topic, no. (% total)

Total Awarded Grants = 17

Supplemental Funding<sup>a</sup> = 11 (64.7)

New Grants<sup>b</sup> = 6 (35.3)

System of care	3 (17.6)	System of care	3 (17.6)
Pain/Quality of life	3 (17.6)	Career Development Award	1 (5.9)
Decision making/communication	2 (11.8)	Decision making/communication	1 (5.9)
Other	3 (17.6)	Pediatric	1 (5.9)

<sup>a</sup>Supplemental Funding is identified as grants/projects ending with a S-suffix (e.g. S1, S2)

<sup>b</sup>New Grants refer to grants/projects that are not supplements

## Discussion

This report focuses on the possible impact that relationship between the COVID-19 pandemic might have had on palliative care and COVID-19 related NIH funding. While only 17 projects met our criteria, there was an increase in the overall percentage of research project grants compared to a 2011–2015 analysis. Research project grants, which are offered to promote innovative health related research and development, made up 58.8% of the total grants in this report, compared to 30.2% in a previous study (HHS, n.d.b). This study also noted a larger percentage of center grants, 23.5% compared to 14.8% (Brown et al., 2018). These center grants, denoted primarily through the P series and U series, are large scale cooperative and networking efforts within the field of palliative care (HHS, n.d.a). In the context of the COVID-19 pandemic, this increase in center related grants may suggest an overarching need for palliative care collaboration nationally and globally.

These results show that three institutes, the NCI, the NINR and the NIA, accounted for around 88% of the total funded grants on COVID 19 Palliative Care research (Table 1). This finding is consistent with previous projects, which noted the same three institutes as the primary funders of palliative care related research (Brown et al., 2018; Gelfman et al., 2013; Gelfman & Morrison, 2008). This continues to support the lack of palliative medicine research funding in other institutes that represent leading causes of death in the United States.

As reported in Table 2, there is an emphasis on health services research/systems of care in both new grants and supplemental funding. Our results also highlight the topics of physical symptom management, and decision making/communication. This data is relatively consistent with prior studies which found a broadening spectrum of palliative care research topics, such as an increase in pediatric studies, 5.9% (2011–2015), and decision making and

communication, 16.9% (2011–2015) (Brown et al., 2018). These three research topics: systems of care, physical symptoms and quality of life, and communication/decision making, correlate with many of the important and necessary skills for the clinical application of palliative care. A European task force investigating recommendations for palliative care during the pandemic concluded that many experts supported flexible ACP, related to decision making and communication, in addition to the treatment of side effects and symptoms of COVID-19 even when the underlying cause had been treated (Janssen et al., 2020). Therefore, these topics accurately reflect the key elements essential to the delivery of high-quality bedside palliative care during a pandemic noted both nationally and internationally.

Previous studies have shown that less than 1% of all NIH grants awarded by the NCI, the NHLBI, the NIDDK, and the NINDS, which represent many leading causes of death, were related to palliative medicine (Brown et al., 2018). Unfortunately, despite the increasing palliative care demand during the COVID-19 pandemic, this study showed that the percentage of NIH awarded COVID-19 grants devoted to palliative care research has not changed. This number remains at less than 1%.

It is clear from these results that while NIH funded COVID-19 palliative care projects correlate well with the palliative care needs at the bedside, the unprecedented demand for palliative care during this pandemic has yet to translate to NIH supported research.

### *Limitations*

There are several notable limitations to this study. Due to the small resulting sample size of this study, one should be aware of a potential increase in the margin of error in this study's results. However, it is important to note that the findings were consistent with previous study outcomes. This provides some support for the validity of these findings. A second limitation is that the only

published paper on NIH funded palliative care research summarized data up until 2015, meaning data used for the comparison group may be slightly outdated. A more recent, pre-COVID-19 funding summary might have allowed for a more accurate examination of the results noted in this paper. Another limitation involved the short time period of this study (from January 2019 to the end of July 2021). Since there is a several month lag between when NIH grants are submitted and approved, it is plausible that this short study period may not have captured all the COVID-19 palliative care grants that are currently being reviewed and processed. The results may be different if the study period had been able to account for this delay. It is likely that an extension of the study period may yield a higher percentage of NIH awarded grants in palliative care. Lastly, since this study reviewed only grants explicitly labeled as palliative care, hospice or end of life, it may have overlooked studies with a palliative care relevant topic not specifically tagged in this manner (e.g., research that specific disease group may have focused on the management of disease specific symptoms).

### **Conclusions**

This study explored whether the COVID-19 pandemic has impacted federally funded COVID-19 palliative care related projects. The results aligned with previous research on palliative care NIH funding, with major funding coming from the same few institutes. Moreover, research topic focus of included grants correlates with bedside clinical needs. Unfortunately, the results of this current study do not indicate that the unprecedented clinical demand of palliative care during the pandemic has increased the percentage of NIH awarded palliative care grants related to COVID-19 (Aaronson et al., 2020). Nevertheless, it is important to note that the short study period as well as the lag between grant submission and approval may have greatly influenced the results. The authors hope that an extended study period in the future will include

funded grants that are in the midst of being processed, thus providing more accurate results. The COVID-19 pandemic has only made clearer what has been known: there is a shortage of specialty-trained clinicians to provide palliative care for patients with serious illness who face distressing symptoms and uncertain prognoses. Although many articles have been published on the role and importance of palliative care during the COVID-19 pandemic, federal support could supply the necessary funds to conduct broader and more in-depth data collection/research. Increased funding for palliative care research has the potential to expand access to palliative care by identifying clinical needs and interventions to address those needs, including models to enhance access to palliative care both during and after the COVID-19 pandemic. Additional research assistance is clearly necessary to support the practice of palliative medicine, especially given the current demand of palliative care across the globe.

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# S-BRATA and Japan: A Novel Art Therapy Framework for the Treatment of ASD and Comorbid SID

Peyton Yamanaka

American School in Japan, Japan

23yamanakap@asij.ac.jp

## Abstract

Children with autism spectrum disorder (ASD) commonly experience low levels of attachment to their parents. This, in turn, causes caregivers to question the efficacy of their own parental skills and increases their rates of stress. In Japan, as in much of the world, the frequency of ASD diagnoses in children is increasing. Interventions like the Program for the Education and Enrichment of Relational Skills (PEERS) have recently been adapted to a Japanese cultural context, but few exist for art therapists. However, Durrani's Sensory-Based Relational Art Therapy Approach is a novel framework that addresses sensory-integration disorder (SID) and impaired attachment directly and thus is a possible intervention for children with ASD in Japan who exhibit impaired attachment to their caregivers. In this paper, the author first discusses in broad terms ASD, art therapy, and their overlap. The author next investigates the status of parents of children with ASD in Japan before examining Durrani's S-BRATA Framework and its seven themes. Finally, the author proposes the adoption of the S-BRATA Framework with cultural adaptations by Japanese art therapists.

## Introduction

Over time, the prevalence of individuals diagnosed with Autism Spectrum Disorder (ASD) has increased (WHO, 2021), and this increase is being particularly felt in Japan (Sasayama et al., 2021). Children and adults with ASD are all unique in their exhibition of symptoms and the

severity of those symptoms. Thus, ASD is a spectrum disorder. In order to address the entirety of the spectrum, interventions aimed to reduce symptoms and improve day-to-day functioning must be tailored to the client. As an example, art therapy is a form of therapy in which an art therapist and a client develop a relationship through creating artwork. Specifically when working with children with ASD, the use of various materials and textures can be effective to address comorbid sensory integration disorder (SID), or an inappropriate reaction to certain external stimuli (Richardson, 2015). In addition to SID, children on the spectrum frequently experience impaired attachment to their caregiver as a result of deficits in social behaviors. However, there is a lack of interventions that use art therapy to confront impaired attachment. Durrani's S-BRATA framework is a recent and novel development that addresses both SID and impaired attachment through art therapy. In this paper, the author first discusses in broad terms ASD, art therapy, and their overlap. The author next investigates the status of parents of children with ASD in Japan before examining Durrani's S-BRATA Framework and its seven themes. Finally, the author proposes the adoption of the S-BRATA Framework with cultural adaptations by Japanese art therapists

## Methods

This paper applies purely correlational research based on categorical observations. It is meant to guide practitioners and suggest further avenues for research, but it is not based upon experimental data and should not be viewed as such.

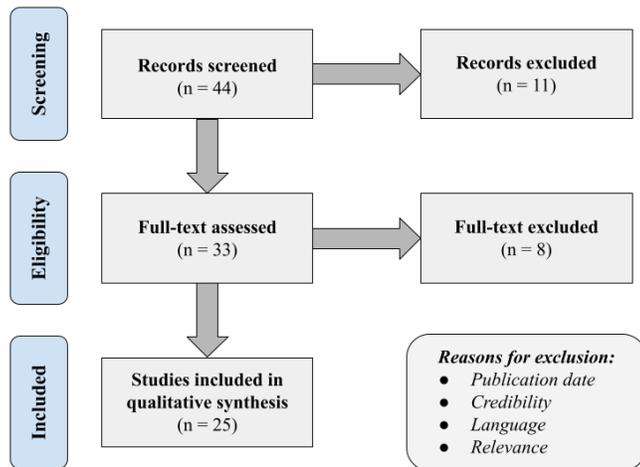


FIGURE 1. PRISMA Flow Diagram showing the vetting process of this systematic review of 43 articles.

## Defining Autism Spectrum Disorder

Effective communication and social interaction are vital for functioning in everyday life. They allow one to express feelings, concerns, emotions, and ideas while also understanding those of others, which consequently helps one develop strong relationships. Autism Spectrum Disorder (ASD) is a developmental disorder which is diagnosed through exhibited “[d]eficits in social-emotional reciprocity... in nonverbal communicative behaviors used for social interaction... [and] in developing, maintaining, and understanding relationships” (APA, 2013, p. 50). Additionally, a person needs to exhibit at least two of the four following attributes:

“[1] Restricted, repetitive patterns of behavior, interests, or activities, as manifested by... stereotyped or repetitive motor movements, use of objects, or speech... [2] insistence on

sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior... [3] highly restricted, fixated interests that are abnormal in intensity or focus... [and 4] hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment” (APA, 2013, p. 50).

While the external appearance of a person with autism is no different from a neurotypical individual, ASD can influence the way one learns, thinks, and acts (CDC, 2020). As the name implies, ASD is a ‘spectrum condition’ and thus affects people to varying degrees, ranging from the need for constant support to complete independence (Autism Society, 2020).

Diagnosis of autism is heavily reliant upon an individual’s behavioral symptoms. Some early symptoms that can be observed include, but are not limited to, avoiding eye contact, a lack of interest in social interactions with friends or caretakers, difficulty verbalizing, and/or getting irritated by minor adjustments to one’s routine (CDC, 2020). Signs of autism generally fall into two categories: those involving communication, social skills, and interpersonal relationships; and those involving restricted and repetitive behavior, patterns, activities, and interests (Autism Society, 2020).

Furthermore, sensory integration dysfunction (SID) and ASD are frequently comorbid in patients. SID is a condition in which an individual responds inappropriately to external stimuli ranging from strange textures to uncomfortable noises (Marco, Hinkley, Hill, & Nagarajan, 2011). SID can make it difficult for people with autism to engage in daily activities and interact in new environments because of an underlying fear of encountering uncomfortable stimuli.

While there is no cure for ASD, several therapies exist intended to support a person with autism function in day-to-day activities (Mayo Clinic, 2018). The goal of certain interventions is to address early symptoms of ASD so that they do not progress because of poor

social experiences (Richardson, 2005). Additional methods may include applied behavioral analysis (ABA), speech therapy, occupational therapy (OT), physical therapy (PT), family therapy, cognitive behavioral therapy, and art therapy.

Autism Spectrum Disorder is a complex condition in which each individual has their own unique needs. The varying degrees and symptoms of autism make approaches to supporting the person and methods of treatment personalized to one's requirements (Martin, 2009). Therefore, it is often difficult to treat ASD, as there are no specific guidelines or medical norms that encompass the entirety of the spectrum.

### **Art Therapy and ASD**

According to the American Art Therapy Association (2017), "Art Therapy is an integrative mental health and human services profession that enriches the lives of individuals, families, and communities through active art-making, creative process, applied psychological theory, and human experience within a psychotherapeutic relationship" (p. 1). Art therapists work with a range of clients who may experience one of various difficulties, disabilities, or diagnoses. Additionally, art therapy is a subjective method of treatment, meaning it is provided depending on the needs of the client (British Association of Art Therapists, n.d.).

Through making art and reflecting on the finished artwork and the creative process, clients can increase their awareness of themselves and others; cope with symptoms (e.g. triggering stimuli), stress, and trauma; enhance cognitive abilities; and enjoy the pleasures and fun of making art (Edwards, 2004). The movement required in art making can trigger different somatic sensations (ability to interpret bodily sensations) and emotional areas of the brain, therefore causing stress-induced reactions that can regulate affect (Hass-Cohen & Findlay, 2015). Paints, in particular, which come in various colors and can be easily manipulated, can

effectively trigger a range of emotions (Edwards, 2004). They also function to stimulate the clients' senses as there are several possible methods of application, and they can be mixed with other materials to create unique textures (Durrani, 2020).

While there is some evidence that supports the benefits of art therapy for clients with ASD, there are still mixed results on its efficacy. There is limited knowledge about the use of art therapy with clients with ASD, and further research is needed to clarify this relationship and improve the field's credibility (Martin, 2009). There is also a lack of quantitative studies in the field; most tend to be qualitative and based on personal interactions (Martin, 2009).

### **Autism and Parenting in Japan**

The need for evidence-based interventions to assist children with autism and their parents in Japan is urgent. In recent studies, researchers have estimated that the prevalence of ASD in Japan is roughly 3.2% (Sasayama, Kuge, & Toibana, 2021). In comparison to the prevalence of individuals with ASD worldwide, which is approximately 0.625%, the numbers are relatively high in Japan (World Health Organization, 2021).

In Japanese culture, conformity and avoiding burdening others are both highly valued and thus, children are expected to act in harmony with others and to learn self-restraint (Asai & Kameoka, 2005). Therefore, being viewed as having a child with problematic behaviours could contribute to increased parenting stress. Moreover, seeking support from one's community, especially in the case of disabilities and mental illnesses, both of which are considered familial problems, is viewed as an act of disruption (Kayama, 2010). While a mother may receive some support from her partner, Japanese husbands are frequently uninvolved in matters relating to children and home (Suzuki et al., 2009). As a result, Japanese mothers carry large domestic responsibilities, likely heightening their stress levels (Sato et al., 2015).

Additionally, Japanese views on parenting emphasize closeness between mother and child as opposed to western parenting norms which push child independence. Thus, when Japanese mothers fail to form a secure attachment to their child with ASD, they are more likely to doubt their identity as a mother (Kayama, 2010). Furthermore, in Japanese society, gender roles suggest that mothers are entirely responsible for taking care of the household and raising their children, and as a result, are frequently shamed for any behavioral issues (Sato et al., 2015). For example, mothers who do not bond strongly with their children may feel that they are to blame and may experience this blame from their peers (Porter and Loveland, 2018).

Family members of children with disabilities often experience stress; however, research points to much higher stress levels in mothers of children with ASD (e.g. Dolev, Sher-Censor, Baransi, Amara, & Said, 2016; Hayes & Watson, 2013). Parenting stress, according to Abidin (1992), is caused by stressors associated with the child domain and the parental domain. Issues relating to the child's behavior and symptoms fall under the child domain whereas parenting characteristics and the level of social support parents receive fall under the parental domain (Porter and Loveland, 2018). Certain symptoms of ASD, a stressor related to the child domain, including sensitivity to physical touch and lack of eye contact can cause a mother to feel less closeness and intimacy with their child. As a result, the struggle to develop a secure mother-child attachment may lead to the self-questioning of their maternal identity (Porter and Loveland, 2018). Additionally, lack of social support and feelings of isolation, a stressor linked to the parental domain, contribute to reduced mental well-being of mothers of children with ASD. A study conducted by Boyd (2002) illustrated how the lack of a support system contributes to maternal depression and anxiety. On the other hand, having a higher level of support correlates

to increased maternal well-being and a more positive relationship with the child.

In an Integrative Review of Parenting Stress in Mothers of Children with Autism in Japan, Porter and Loveland (2018) demonstrated how Japanese mothers of children with ASD experience elevated levels of parenting stress similar to their Western counterparts. Further, child behaviour problems and low levels of social support, the causes of such high levels of parenting stress in Japanese mothers of children on the spectrum, are consistent with those of Western countries (Porter and Loveland, 2018). However, in addition to these stressors, this study provided evidence that Japanese cultural norms and views on parenting play a significant role in increasing parenting stress in mothers of children with autism. The review found that parenting stress is heightened when the child's intellectual ability is higher. When the child with ASD is intellectually able, others who do not know the child may not recognize that they have a disability. Thus, the child with ASD may be held to expectations that are greater than those placed upon children who exhibit more noticeable symptoms of ASD (Davis & Carter, 2008).

### **S-BRATA and Its Seven Themes**

While treatment options for ASD in art therapy are limited, certain recent interventions have shown potential. Among these, Durrani's (2019) Sensory-Based Relational Art Therapy Approach is unique in that it specifically addresses comorbid Sensory Integration Disorder (SID) and impaired attachment exhibited in ASD. The S-BRATA is a framework intended to guide art therapists who work with children with ASD in supporting their diverse needs (Durrani, 2019). However, it can be applied to all forms of multisensory kinesthetic therapy, including all types of play therapy, due to its flexibility (Durrani, 2020). Beyond that, parents and guardians can also work with art therapists to use the S-BRATA framework to support their children. The S-BRATA framework is structured around seven

themes, as seen in Figure 1. Durrani (2019) further notes that these themes can be adjusted to each child's needs regardless of domain.

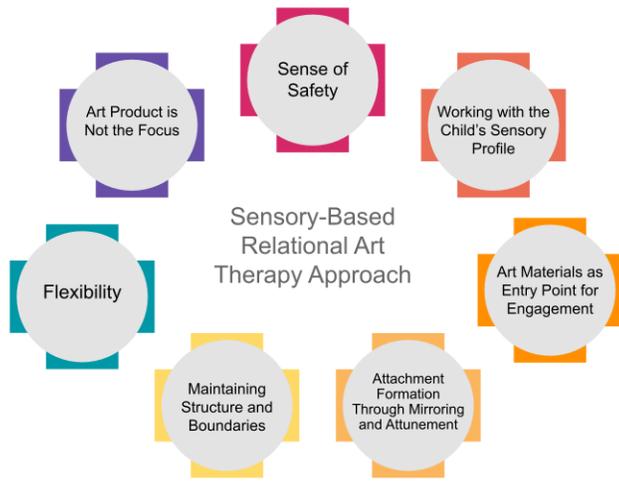


Figure 1: S-BRATA Framework.

*Sense of Safety*

Though she begins with the sense of safety, Durrani (2020) highlights that the 7 themes do not occur in a fixed order but rather run hand in hand with one another. When working with a child with ASD and comorbid SID who experiences high levels of anxiety, it is crucial to establish a safe environment. If a child feels uncomfortable in their surroundings, they are disengage in order to avoid potential threats or traumas (Durrani, 2020). In order to achieve a sense of safety, Durrani advises art therapists to hold back and make art themselves. Holding back is the concept of avoiding actively engaging with the client by, for example, making art to draw the child's attention, until they feel ready to participate without feeling threatened (Durrani, 2020). This is particularly important because children with ASD and SID are likely to experience elevated levels of stress (Gillott & Standen, 2007).

*Working with the Child's Sensory Profile*

Children with ASD and comorbid SID may respond atypically to specific external stimuli that

cause pain or anxiety (Camarata, Miller, & Wallace, 2020). In order to prevent causing unintended anxiety to the child, it is highly necessary for the art therapist to become familiar with the client's sensory profile prior to entering therapy sessions (Durrani, 2020). If a child is not assured that they will not encounter any uncomfortable stimuli, they are likely to disengage and close off as a means of protecting themselves (Camarata, Miller, & Wallace, 2020). Thus, the themes of sense of safety and working with the child's sensory profile go hand in hand, as understanding how a child reacts to certain stimuli is a gateway into creating a safe environment.

*Mirroring and Attunement*

The mirror neuron system (MNS) is triggered when one watches another person complete an action, and mimics that same act. Through mimicking, it is suggested that one can understand another's intentions or state of mind (Kilner & Lemon, 2013). However, studies have shown that individuals with ASD have an impaired MNS, thus presenting and intensifying relational challenges for people on the spectrum (Gallese, 2005; Oberman, Pineda, & Ramachandran, 2007). It can be suggested that "mirroring or reflecting back to the child with ASD not only promotes attachment, it may also have a positive impact on the development of the MNS," though this claim remains under-researched (Durrani, 2020).

*Art Materials as Entry Point*

This theme addresses both SID in children with ASD and impaired attachment (Durrani, 2020). There are a wide variety of art materials, both traditional—paints, clay, and pencils—and non-traditional—shaving foam and slime—that provide different textures and visceral qualities (Edwards, 2004). Additionally, the lure of art materials can encourage children to engage with the art therapist, thus laying the foundation for a relationship between the client and the therapist (Richardson, 2015). Taking into consideration the

sensory profile of the child, the art materials can be used to both minimize stress as well as encourage reserved clients to engage in the session, though loose materials such as paint and foam should be used judiciously as they may cause dysregulation or discomfort to children who are hypersensitive to physical stimuli (Durrani, 2020). Moreover, systematically exposing the child to unique textures and art materials is suggested to both decrease extreme sensitivity to certain tactile sensations and improve behaviors and skills that are interrupted by tactile over-responsivity (Camarata, Miller, & Wallace, 2020)

### *Maintaining Structures and Boundaries*

Art therapists can use both directive and non-directive approaches when working with children with ASD (Kottman, Dickinson, Meany-Walen, 2017). In order to create a safer atmosphere for the child, an art therapist may take a non-directive approach, allowing the client to lead the session without feeling forced or threatened (Durrani, 2020). On the other hand, taking a directive approach involves the therapist preparing a plan and goals for the client, which creates a more structured session (Durrani, 2020). Though a directive approach may be useful, the session can quickly become overwhelming for the client. Thus, a therapist might engage in a non-directive approach instead (McNeilly, 1983). While the S-BRATA is not considered a highly structured approach, structure and boundaries should be incorporated to some extent to control certain behaviors, as children with ASD may experience anxiety when routine is absent (Durrani, 2020).

### *Flexibility*

Durrani (2020) states that “[t]he need for flexibility across all the themes of the S-BRATA [is] increasingly apparent due to the complexity of the spectrum and the unpredictability of each child’s response from one session to the other” (para. 2). Because ASD is a spectrum disorder, each child requires different levels and types of support, and thus, flexibility is necessary to accommodate their

needs (Autism Society, 2020). Flexibility in art-making, or not restricting artwork to a particular area or medium, allows the children to take part in the session on their own terms rather than forcing them to participate (Edwards, 2004). Flexibility also entails, at times, substituting art materials with other toys with unique textures, sizes, and colors to both address sensory regulation and keep the child motivated and engaged while working with the therapist (Durrani, 2020). Furthermore, the behavior of children with ASD is often unpredictable, thus making flexibility necessary in order to address such behaviors (Autism Society, 2020).

### *Art is Not the Focus*

The process of art-making heavily revolves around exposing the child to different materials and textures in order to address sensory regulation (Durrani, 2020). Though the process of mark making and experimenting with art tools and materials is often the focus of the sessions, it is still very much possible for the final product to hold some symbolic value (Edwards, 2004). However, Durrani (2020) states that when working with children at the lower end of the spectrum, the final artwork often does not carry much value, as the sensory experience of artmaking is foremost.

### **The Need for S-BRATA in Japan**

In Western countries, mothers of children with ASD experience high levels of parenting stress due to factors relating to behavioral characteristics of the child as well as the lack of social support (Porter and Loveland, 2018). Boyd (2002) found that lower levels of support is associated with maternal depression and anxiety and impaired attachment to the child with ASD. Particularly in Japan, where approximately 3.22% of 5-year-olds have ASD (Iwasaki, 2020), mothers of children on the spectrum demonstrated high levels of parenting stress caused by factors related to both the child and parent domains as in Western countries (Porter and Loveland, 2018).

However, cultural norms and strong views on parenting also play an important role in increasing parenting stress, which in conjunction with impaired attachment related to ASD, affects Japanese mothers (Porter and Loveland, 2018). While other psychological interventions are being introduced to confront ASD in Japan, Durrani's S-BRATA framework explicitly addresses sensory integration disorder and its effects on impaired attachment. Additionally, other approaches are not targeted toward the well-being of parents (Porter and Loveland, 2018). Therefore, the author proposes the adoption of Durrani's S-BRATA framework to address impaired attachment between child with ASD and mother in Japan.

However, it is important to consider that the S-BRATA framework was developed in Singapore and needs to be translated into a Japanese cultural context. Cultural differences affect the way emotions are recognized. For example, in Japan, people tend to focus more on one's eyes when determining sadness or happiness whereas in Western countries, people rely more upon the mouth (Yuki, Maddux, & Masuda, 2007). Similarly, social norms in Japan differ from other nations, such as the United States.

An example of an intervention that was translated to suit Japanese participants was the Program for the Education and Enrichment of Relational Skills (PEERS) originally developed in the United States. In order to adapt the PEERS intervention to suit Japanese culture, the following steps were taken: 1) program was translated into Japanese by practitioners, 2) non-practitioner translators reviewed the translation, 3) a trial experiment was hosted and the intervention was adjusted based on feedback, and 4) the researchers observed Japanese teens for cultural norms and adjusted the framework as needed (Yamada, 2019). The results of the study "indicated that with minor cultural changes, PEERS is effective in improving social skills related to making and keeping friends for adolescents with ASD in Japan." (Yamada, 2019, para. 46). Similarly, S-BRATA might be

adapted through the consideration of specific media commonly found in Japan and awareness of cultural norms in social interactions. This needs to be developed in conjunction with Japanese families and art therapists who know the situation best.

## Conclusion

The frequency of ASD diagnoses in Japan is exceptionally high. While interventions using traditional clinical psychology methods are being explored, art therapy remains underutilized as a treatment for Japanese people with ASD. Furthermore, levels of parenting stress are elevated among Japanese mothers of children with ASD due to factors relating to the child's problem behaviors, the lack of social support, and cultural views on parenting in Japan.

Thus, Durrani's S-BRATA framework, with minor adjustments to make it appropriate to a Japanese cultural context, should be adopted by practitioners of art therapy in Japan to address the growing number of people with ASD. The S-BRATA model, in addition to confronting comorbid SID and impaired attachment, may also address the extremely high levels of stress among Japanese mothers. It is the author's hope that this paper guides art therapists in Japan as they expand their practice to be more inclusive of their clients' needs.

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# Rice Leaf Disease Classification Using Deep Transfer Learning Convolutional Neural Network: MobileNet + Bidirectional GRU

Sarah Yim

Seoul International School, South Korea  
sarahyim2023@gmail.com

## Abstract

Agriculture, the supporting backbone to the economic growth of many countries, has played a significant global role in the economy. With rapid technological advancements in various fields today, it is important to invest time and effort into developing advanced methods to preserve agricultural practices. However, the lack of technology and expertise in crop disease identification is a notorious problem troubling the agricultural industry, especially in developing countries. This often leads to severe crop loss and waste, affecting not only farmers' yield but also consumers' food intake. Rice leaf disease identification, in particular, rises as an important issue as rice is a staple food for a large proportion of the global population. Specifically, timely and accurate diagnosis of rice leaf diseases is crucial. To address this issue, this paper implements an image-based deep learning approach to identify and classify rice leaf diseases presented in a dataset derived from a rice field in Sherta located in Gujarat, India. This dataset contains 120 images belonging to three distinct classes: Brown Spot, Leaf Smut, and Bacterial. Evaluation performances followed by statistical analysis are conducted using eight different convolutional neural network (CNN) models: Inception V3, Vgg16, Vgg19, MobileNet, DenseNet121, ResNet101, NASNetMobile, and MobileNet+Bi-GRU. The best performing model was the MobileNet+Bi-GRU model with an accuracy score

of 87.24%. The experimental results from the performance evaluations revealed great potential in incorporating deep learning techniques for rice leaf disease identification and classification.

*Keywords:* agriculture, rice leaf disease identification, deep learning

## Introduction

### *Background:*

Rice, a starchy cereal grain and grass species *Oryza Sativa*, is a staple food for roughly half of the world's population. With more than 90% of rice grown in Asia, practically all of East and Southeast Asia are dependent on rice as a staple food. Rice yields vary with different conditions, ranging from 700 to 4,000 kilograms per hectare (Encyclopedia, 2021). India, a global agricultural powerhouse with leading production in milk, wheat, and rice (India Brand Equity Foundation, 2021), ranks second highest in rice production after China, producing about 110 million metric tons of rice per year (Vukotić et al., 2016). Agriculture is a livelihood for approximately 58% of India's population.

With the growing world population, global rice demand continues to increase; with a global rice demand of 439 million tons in 2010, 496 million tons in 2020, to a predicted 555 million tons in 2035, projections speculate a demand increase of 26% in the next 25 years. Hence, it is highly likely the 150 million hectares of rice fields

available around the world will not suffice for the rice demands in the next few years. Because land is scarce and expansion is unlikely, global rice yields must increase at faster rates of at least 1.2-1.5% over the next decade, equivalent to 8-10 million tons more paddy rices each year (Ricepedia, n.d.). However, this is extremely difficult due to the frequent damages that are overlooked in paddy fields from various diseases, pesticides, and poor harvest management. Every year, farmers lose approximately 37% of their rice crops from diseases and pests (Rice Research, n.d.). In the world's most agricultural regions and developing nations, unsustainable and deficient rice management results in decreasing merchantability and rice yield, thereby increasing malnutrition and poverty. To make matters worse, many farmers lack expertise in agricultural management, hence cannot detect or identify the potentially harmful diseases in their rice crops. In response to the exacerbating dilemma of rice diseases, farmers today utilize digital agriculture such as Artificial Intelligence (AI), Satellite Imagery, and Machine Learning, and other advanced analytics resulting in higher crop yield

and more efficient crop management. In particular, in collaboration with Microsoft, farmers in India have implemented artificial intelligence and machine learning based sowing advisories that send automated voice calls that inform farmers on the optimal date to sow and alerts prior to pest infestation. Another innovation is the multivariate agricultural commodity price forecasting model to predict crop yields, prices, and commodity arrivals at every farming stage. This model uses input data from remote sensing, geo-stationary satellite images, weather, and other datasets to predict measurements with accuracy (Microsoft India, 2017). Artificial intelligence and machine learning have only recently marked their potential in agriculture. Such forms of digital agriculture have great prospects in providing stability for agricultural communities, especially in agriculture-dependent developing nations such as India. Additionally, with far-reaching impacts of climate change on a global scale today, digital agriculture is more imperative than ever before. The graph below shows the total rice consumption worldwide from 2008/2009 to 2020/2021 (Shahbandeh, 2021).

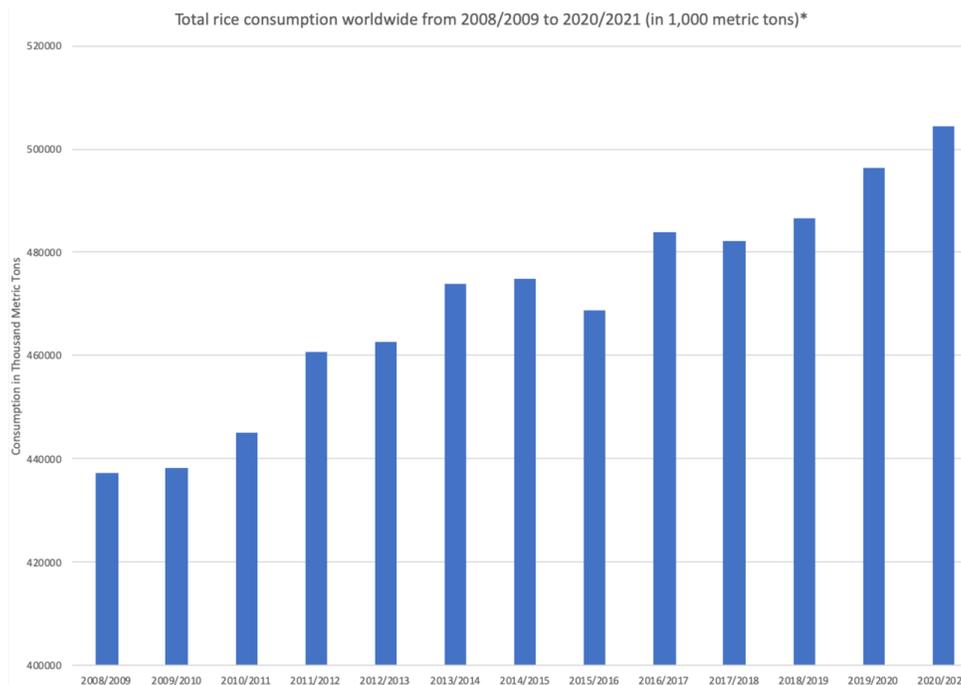


FIGURE 1: Total rice consumption worldwide from 2008/2009 to 2020/2021

### *Objective*

The objective of this research is to complement rice productivity through early prediction of rice leaf diseases such as bacterial blight, leaf smut, and brown spot diseases. With early alertness, farmers could take precautions to manage the spread of diseases to other crops, saving several tons of rice from going to waste and increasing total rice yield and merchantability. To do so, deep learning frameworks such as Inception V3, Vgg16, Vgg19, MobileNet, DenseNet121, ResNet101, NASNetMobile, and MobileNet+Bi-GRU were employed to detect potential rice diseases in rice crops. Next, a comparative study analysis of the performance of each algorithm was conducted. Lastly, utilizing Gradient-weighted Class Activation Mapping (Grad-CAM) and the heatmap feature, images could be processed and visualized, identifying notable patterns. This would overcome the limitations of deep learning's black box model, thereby increasing the study's applicability in agriculture.



FIGURE 2: Visualization of the given image

### *Related Works*

In this section, previous work on incorporation of deep learning and neural networks on rice disease identification and classification, along with the accuracy scores for each algorithm, are discussed.

In literature, numerous research papers have been published for rice disease identification and classification such as using support vector machines, automated feature engineering, comparisons of various deep-learning models, and transfer learning of deep convolutional neural networks.

Firstly, Sethy et al. carried out performance evaluations of 13 number CNN models in transfer

learning and deep feature plus support vector machine (SVM) approach. Sethy et al. classified four types of rice-leaf diseases, namely bacterial blight, blast, brown spot and tungro. Because the feature of fc6 had the most significant correlation towards classification compared to fc7 and fc8 features of AlexNet, vgg16, and vgg19, only fc6 was considered when choosing the best classification model. Next, through statistical analysis of accuracy, sensitivity, specificity, FPR, F1 score, and training time, Sethy et al. concluded that the ResNet50 plus SVM model was the best classification model in the deep feature approach, while in the transfer learning approach, no statistical difference among the CNN models were exhibited. Among the small CNN models and comparable to the ResNet50 plus SVM model was the deep feature of mobilenetv2 plus SVM (Sethy et al., 2020).

Das et al. developed a deep-learning based automated feature engineering for early rice leaf disease prediction for diseases such as leaf blast, brown spot, and bacterial leaf blight. After images portraying specified portions of various rice leaf diseases were identified from a dataset of 10,500 infected leaves, they were fed into the convolution neural network (CNN) model consisting of four convolution layers, two fully connected layers, and one softmax output layer. Performance evaluations were conducted to assess the effectiveness of each classifier for rice leaf disease prediction. It was observed that the CNN, NB, and LR showed relatively better performance than other classifiers, having accuracy scores of 91.07%, 92.16%, and 90.35% respectively. Next, Das et al. compared the CNN classifier with other rice disease classifiers from previous works, depicting how the CNN method nonetheless had superior performance than all the other classifiers (Das et al., 2020).

Burhan et al. performed five different deep learning models (Vgg16, Vgg19, ResNet50, ResNet50V2, and ResNet101V2) using an artificial data set classified into four classes, namely Hispa, Healthy, Brown Spot, and

LeafBlast, and a binary classification of Healthy Vs. Unhealthy using a dataset of images from rice fields in Pakistan. From the experiment using the artificial data set, the ResNet50, demonstrating an accuracy score of 75.0, showed the best performance. From the experiment using the real data set, ResNet101V2, demonstrating an accuracy score of 86.799, showed the best performance. However, limitations such as having a limited number of images in the datasets and visible shadows in many of the images hindered the efficiency and reliability of the results (Burhan et al., 2020).

Shrivastava et al. utilized a pre-trained deep convolutional neural network (CNN) and support vector machine (SVM) as their feature extractor and classifier, respectively. Experiments were conducted with varying ratios of training-testing sets, and the training-testing division of 80%-20% demonstrated the highest classification accuracy of 91.37% (Shrivastava et al., 2019).

Lu et al. proposed a novel rice disease identification disease method based on convolutional neural network (CNN) techniques. CNNs were trained to identify 10 rice diseases using 500 images portraying healthy and diseased rice leaves/stems. The proposed model had an accuracy score of 95.48%, much higher than that of conventional machine learning models such as the BP, SVM, and particle swarm optimization (PSO) methods (Lu et al., 2017).

## Methods

### *Data Description*

This rice leaf diseases dataset, obtained from the Shertha locality in Gujarat, India and uploaded on Kaggle, contains images of disease-infected rice leaves, each belonging to one of three classes i.e. Brown Spot, Leaf Smut, and Bacterial Leaf Blight. Bacterial blight, caused by *Xanthomonas oryzae*, is one of the most serious diseases in rice. The bacteria spreads through ooze droplets on lesions of infected plants and normally causes wilting and yellowing of leaves. The earlier the disease occurs, the higher the yield loss (Rice Knowledge

Bank, n.d.). Leaf smut, a fungal disease caused by fungus *Entyloma oryzae*, is a widely distributed rice disease that produces angular, black spots on both sides of the leaves. The fungus is spread by airborne spores and over winters in soil, particularly in diseased leaf debris. Brown spot is a fungal disease caused by fungus *Cochliobolus miyabeanus* that infects coleoptiles, panicle branches, glumes and grains. It results in brown, circular spots on coleoptile leaves of seedlings, indicating plant inability to use nitrogen and weakened plants (Groth & Hollier, n.d.).

With a total of 120 rice leaf disease images in the dataset, 40 images account for each class. The leaves in these images are derived using a digital camera and empirical evaluation for background removal and segmentation (Prajapati et al., 2017). This was a very convenient and accessible dataset, for all images had a uniform, clean background with one leaf in each image.

### *GRU*

GRU was proposed by Cho et al. in 2014 and its architecture is similar to long short term memory(LSTM). LSTM was developed to solve the existing problem of recurrent neural network(RNN). RNN suffers from a vanishing gradient problem; first received information has a strong influence on learning and then gradually diminishes, eventually failing to influence learning. Cell state from the LSTM prevents that drawback by storing previous steps of information in a memory cell and sending it out. The cell state utilizes three gates : input gate, forget gate and output gate to determine whether the information is reflected. The GRU consists of two gates : reset gate and update gate. The reset gate determines whether to combine the new input with previous memory and the update gate determines the amount of the memory to remember. The overall computational process of the GRU is carried out with the following formulas (Cho et al., 2014):

$$rt = \sigma(Wrht-1, xt + br) \quad (1)$$

$$ht = \tanh(Whrht-1, xt + bh) \quad (2)$$



bidirectional GRU to train the whole parameters more efficiently.

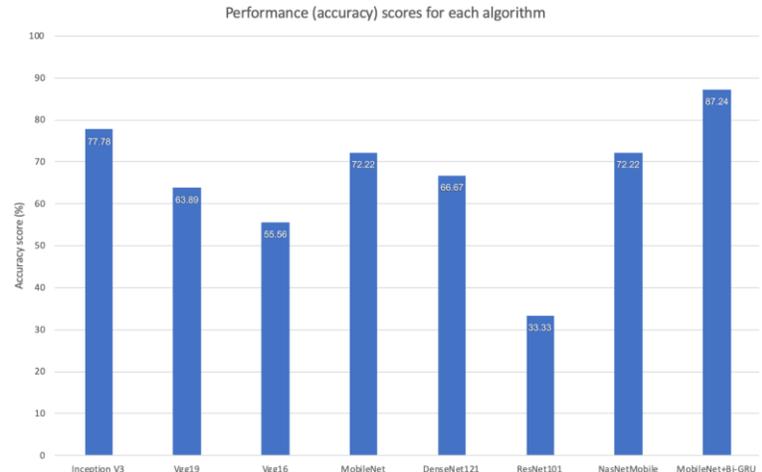
FIGURE 5: Summary of the MobileNet architecture

Type / Stride	Filter Shape	Input Size
Conv / s2	$3 \times 3 \times 3 \times 32$	$224 \times 224 \times 3$
Conv dw / s1	$3 \times 3 \times 32$ dw	$112 \times 112 \times 32$
Conv / s1	$1 \times 1 \times 32 \times 64$	$112 \times 112 \times 32$
Conv dw / s2	$3 \times 3 \times 64$ dw	$112 \times 112 \times 64$
Conv / s1	$1 \times 1 \times 64 \times 128$	$56 \times 56 \times 64$
Conv dw / s1	$3 \times 3 \times 128$ dw	$56 \times 56 \times 128$
Conv / s1	$1 \times 1 \times 128 \times 128$	$56 \times 56 \times 128$
Conv dw / s2	$3 \times 3 \times 128$ dw	$56 \times 56 \times 128$
Conv / s1	$1 \times 1 \times 128 \times 256$	$28 \times 28 \times 128$
Conv dw / s1	$3 \times 3 \times 256$ dw	$28 \times 28 \times 256$
Conv / s1	$1 \times 1 \times 256 \times 256$	$28 \times 28 \times 256$
Conv dw / s2	$3 \times 3 \times 256$ dw	$28 \times 28 \times 256$
Conv / s1	$1 \times 1 \times 256 \times 512$	$14 \times 14 \times 256$
5× Conv dw / s1	$3 \times 3 \times 512$ dw	$14 \times 14 \times 512$
Conv / s1	$1 \times 1 \times 512 \times 512$	$14 \times 14 \times 512$
Conv dw / s2	$3 \times 3 \times 512$ dw	$14 \times 14 \times 512$
Conv / s1	$1 \times 1 \times 512 \times 1024$	$7 \times 7 \times 512$
Conv dw / s2	$3 \times 3 \times 1024$ dw	$7 \times 7 \times 1024$
Conv / s1	$1 \times 1 \times 1024 \times 1024$	$7 \times 7 \times 1024$
Avg Pool / s1	Pool $7 \times 7$	$7 \times 7 \times 1024$
FC / s1	$1024 \times 1000$	$1 \times 1 \times 1024$
Softmax / s1	Classifier	$1 \times 1 \times 1000$

## Results

The deep-learning software library Keras was used to calculate and evaluate the performances of the models. Using Google Colab along with GPU as the hardware accelerator, the rice leaf diseases dataset was imported onto Google Drive and mounted onto Google Colab. The performance of each algorithm for rice leaf disease classification was measured and evaluated in terms of accuracy, and a comparative study analysis of the performance was conducted. Figure 7 shows the average accuracy scores of different performing models. The best performing model was MobileNet+Bi-GRU with an accuracy score of 87.24%. The poorest performing model was ResNet101 with an accuracy score of 33.33%.

The Figure 8 graphs display that initially, although the accuracy was relatively low and loss was relatively high, upon increasing the number of epochs, the loss notably decreased while the accuracy increased. The greater the accuracy and smaller the loss, the better the classifier



models are at modeling the correlations between the inputs and output targets with fewer errors.

FIGURE 7: Comparison of performance scores for each algorithm

RGB colorized heatmaps were created for the three rice leaf disease images, i.e. Brown Spot, Leaf Smut, and Bacterial, to colorize the intensity of the heatmap and identify the area in each leaf in which the disease was most dispersed. From a color scale of purple to red exhibiting lower to higher intensity of disease dispersal, performing heatmaps allowed for a more specific and accurate identification of the leaf's location in which each disease was found. The heatmap for the Brown Spot and Bacterial rice leaf disease image indicated that the inner center of the rice leaf was most infected with the disease, whereas the heatmap for the Leaf Smut rice leaf disease image indicated that the top center half was most infected with the disease. Areas depicted with lower color intensity level such as blue or purple indicated areas of less infection by each disease.

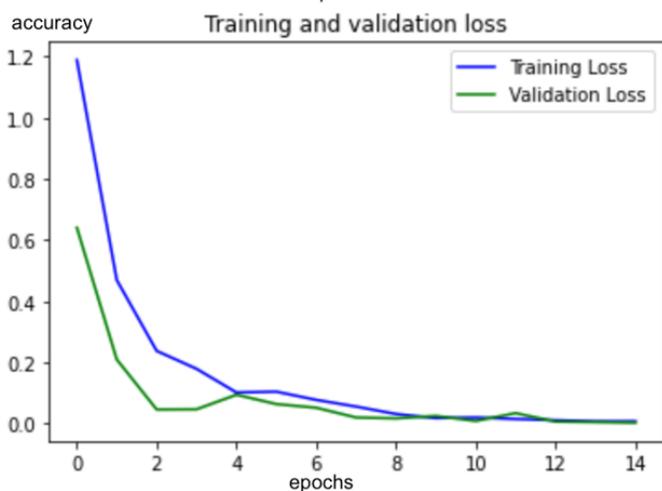
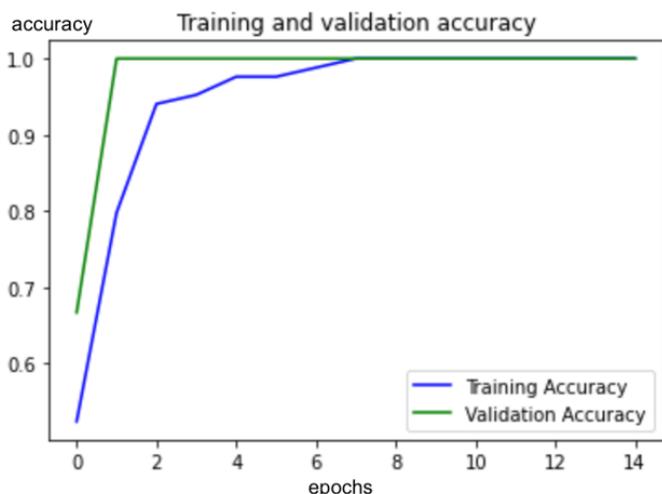


FIGURE 8: Accuracy and loss graph for training and validation set

## Discussions

### Principle Finding

After evaluating the performances (accuracy scores) of the eight different CNN models, i.e. MobileNet+Bi-GRU, Inception V3, Vgg16, Vgg19, MobileNet, DenseNet121, ResNet101, and NASNetMobile, to determine the best performing model for identification of rice leaf diseases, it was revealed that performances from best to worst were MobileNet+Bi-GRU, Inception V3, MobileNet and NasNetMobile, DenseNet, Vgg19, Vgg16, ResNet101, in that order. Overall, among all the CNN models, MobileNet+Bi-GRU demonstrated the best performance with the highest accuracy score of 87.24%.

Our accuracy score of the best performing model (MobileNet+Bi-GRU), 87.24%, is relatively high compared to other related works. For example, when Burhan et al. performed five different deep learning models for multiclass rice leaf disease classification, the accuracy score of his best performing model (ResNet50) was 75.0% (Burhan et al., 2020). This may be because the images in our dataset consisted of more clear, unshadowed images contributing to higher efficiency and reliability of the results, compared to many other related works utilizing indistinct, shadowed rice leaf images.

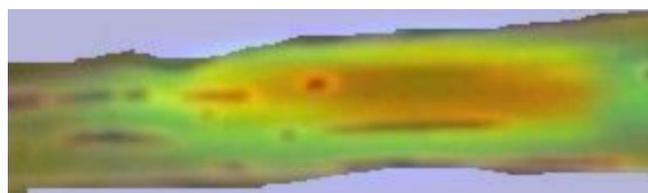


FIGURE 9: Heatmap of Brown Spot rice leaf disease image

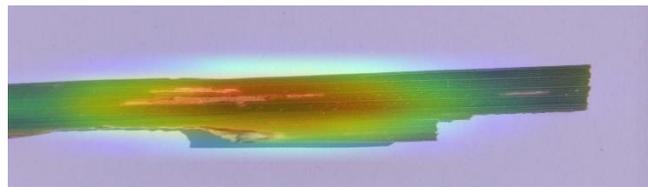


FIGURE 10: Heatmap of Leaf Smut rice leaf disease image

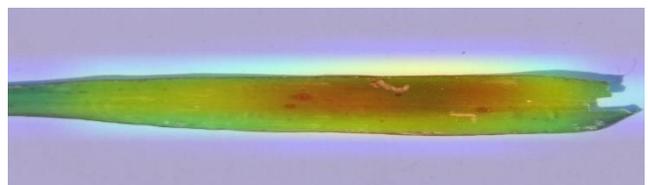


FIGURE 11: Heatmap of Bacterial rice leaf disease image

### Limitations

One limiting factor in this Indian dataset was its small size. This dataset consisted of 120 images of disease infected rice leaves, with only 40 images in each class. With more images to represent each class in the dataset, the model could extract each class' features more precisely,

possibly increasing the accuracy scores for the performing models.

Another limitation of the dataset was the fact that out of the many more rice leaf diseases found in rice crops, only three types of rice leaf diseases (brown spot, leaf smut, and bacterial) were identified. Although these three may have been the most prominent ones found in the area in which this dataset was collected, the Shertha rice field in Gujarat, India, many more types of rice leaf diseases such as eyespot and sheath rot could be included in the dataset for broader application.

In this study, the accuracy scores did not go over the score of 90(%), possibly because of the small size of the dataset or the limited number of rice leaf diseases identified in the dataset. This limited the ability of the models to classify the rice leaf disease images into their respective classes with accuracy and precision.

Finally, only image classification was performed with the images in this dataset, limiting us to classification of what was contained in each image. An improvement would be to perform object detection as the next step, helping specify the location and identify the object in each image more thoroughly and quickly. This would especially be convenient when using a mobile application, for images uploaded into the application could be processed and checked in real time for fast and efficient classification of rice leaf diseases for farmers.

## Conclusions

In this paper, deep learning techniques were utilized to classify rice leaf diseases. Eight distinct CNN models were applied to the rice leaf diseases dataset from Shertha in Gujarat, India. The experiments were conducted by portioning the dataset into a training-testing ratio of 70%-30%. The best proposed model, MobileNet+Bi-GRU, was able to classify rice leaf diseases with a classification accuracy score of 87.24%, whereas the worst performing model, ResNet101, was able to classify rice leaf diseases with a classification accuracy score of 33.33%. With a

larger dataset constituted of various types of rice leaf diseases globally found, MobileNet+Bi-GRU with a 70%-30% training-testing ratio could be a remarkably resourceful model to deploy for rice leaf disease classification in rice fields.

With the statistical analysis of the performances conducted in this study, we can conclude that applying deep learning algorithms to rice leaf disease classification and digital agriculture as a whole is a potential solution to decrease rice loss and increase global rice productivity to meet the increasing global rice demand. This approach can also be further incorporated into a mobile application for farmers, especially in developing countries with poor crop management technology. Deep neural networks are often criticized for being a black box model which makes the process between the input and output untraceable, thereby limiting the practicality when applied to applications. However, this study overcame that limitation by utilizing Gradient-weighted Class Activation Mapping (Grad-CAM) to better understand the model's predictions and facilitate the applicability to agriculture. The application could scan images of rice crops and not only detect diseases that may have infected the crops but also identify the specific area of infection, establishing advanced agricultural technology. With digital agriculture in its nascent stage today, it is crucial that more researchers implement artificial intelligence to more effectively address problems in the agricultural industry.

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# Stress and Isolation: The Effects of a Remote Learning Environment on Adolescent Emotional Development

Kevin Zhang

Stuyvesant High School, United States

kevinzhangkang@gmail.com

## Abstract

With approximately 1.6 billion of the world's student population having their norm completely altered and lives uprooted as a result of the COVID-19 pandemic, their emotional health should be of the utmost importance. Emotional health was often disregarded in the past but in our modern times, the immense stress caused by an abrupt shift toward a remote environment can greatly affect the emotional development of adolescents and have long-term effects on their emotional wellbeing well through adulthood. The stress, anxiety, and changes in environment and personal habits can greatly influence the way an adolescent lives their lives, from emotions they experience, to their social interactions. The result is that the stressors caused by a remote environment decrease social interaction and increase negative emotions and psychological disorders, leading to an impairment in the emotional development in adolescents that can have long-lasting effects.

*Keywords: Remote Learning, Remote Environment, Adolescents, Emotional Development, Social Isolation*

## Introduction

In early 2020, 1.6 billion students shifted to remote learning as a result of the COVID-19 pandemic in order to continue learning (Bonnell et al., 2021). While this new virtual environment allowed normal education to continue relatively normally, the emotional wellbeing of students was

not made a priority. Schools are a familiar environment to students, similar to a home, and with traditional schools no longer in session, students were forced to stay home, placing them in a new environment with new factors, risks, and challenges, some of which could affect their emotional wellbeing and development (Mohammed). While COVID-19 itself is not at the forefront of concerns for children, the social-emotional influences and changes in their environment can cause hardships (Buheji et al., 2020). Adolescents are especially prone to some of the indirect risks that stem from the virtual environment as a result of the pandemic, and challenges due to disruption of normal companionship and human interaction can greatly alter the mindsets of children and adolescents, leading to stress, disorders, and even suicide attempts (Buheji et al., 2020). Research specifically regarding the impact of a remote environment on adolescent emotional development has not been done to the extent of our knowledge.

## Methods

COVID-19 is a novel concern, with research about it and its effects being relatively recent. A search through online databases such as Google Scholar, PubMed, NCBI, and ProQuest showed that some surveys about the effects of the COVID-19 pandemic and research about the effect the pandemic has had on children and adolescents have been done. An analysis of how remote environments have affected the emotional

development of adolescents was conducted by searching through online databases with variations of “remote learning”, “remote environment”, “emotional development” and “adolescents”. Articles containing research on young children and adults were excluded.

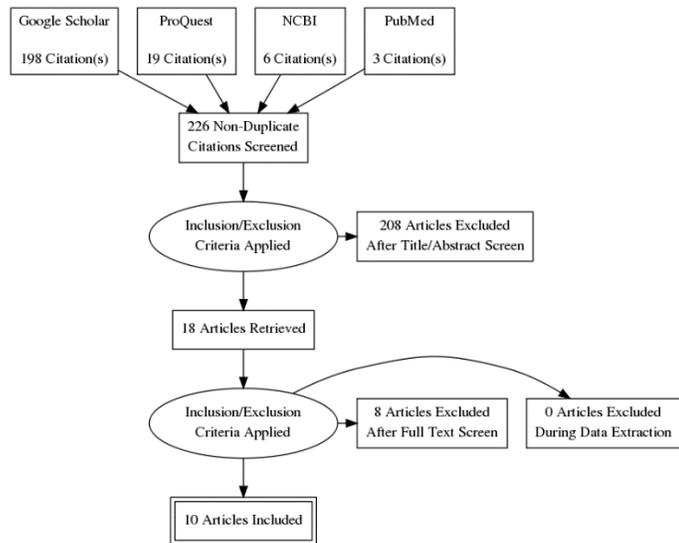


FIGURE 1: PRISMA Flow Diagram illustrating the systematic review of 226 articles reviewed in this study

## Results

### *Family Relations*

In a remote environment, children are much more likely to interact with their family daily and be closer to family issues and conflicts. If family issues are present in a household, the stress a child may feel can be exacerbated. Surveys conducted in Spain and Italy of parents’ perception of their children’s emotions indicated that 76.6% of parents reported difficulty concentrating, 52% reported boredom, 39% reported irritability, and 38% reported nervousness. Teenagers feeling lonely or secluded may experience consistent unhealthy thoughts and additional conflict with family (Buheji et al., 2020). The pandemic has resulted in more stress for parents and adults as well, which may affect instances of domestic violence (Buheji et al., 2020). Parental stress can cause parents to

be less likely to notice their children’s struggles and a lack of emotion-oriented conversations can cause doubts and anxiety to develop (Panicker & Nedungottil, 2021). Familial relationships within a household greatly impact children, especially in a remote environment. Parents are the role models of their children, and in a remote environment, the effect their actions have are magnified. Improved interactions between parent and child can lead to a greater sense of self-sufficiency (Panicker & Nedungottil, 2021).

### *Lack of Social Interaction*

With schools closed and a new remote environment, the opportunities adolescents have to socialize and interact with friends and other people have been greatly diminished. Loss of support during this critical period of development can lead to “lockdown loneliness”, a risk factor of mental health during the pandemic (Glasper, 2021), and loneliness can be attributed to elevated levels of anxiety during the pandemic (Zhao et al., 2021). An Australian Report found that missing important school milestones and a reduction in social interaction have caused high levels of psychological distress (Glasper, 2021). Social activities and interactions with friends provide an outlet for emotions. Without these, adolescents can be susceptible to frequent outbursts of anger, anxiousness, and feelings of isolation. Under extreme stress, they are prone to impulsive decisions and impaired judgment (Panicker & Nedungottil, 2021). The suppression of emotions is associated with negative effects, higher dropout rates, and higher levels of anxiety (Zhao et al., 2021). With less social interaction, and consequently fewer outlets for adolescents to express emotion, they can be released in unhealthy ways or suppressed, leading to more negative emotions and detrimental effects.

### *Remote Learning*

The emotional wellbeing of students was once thought to be inhibiting to the education of students, but studies have found the contrary to

be true. The educational experience and emotions of students are very much intertwined with one another (Zhao et al., 2021). In a remote learning environment, students may sometimes struggle academically, with some students falling up to a full year behind (Glasper, 2021). While many parents supported the closure of schools, a study in the UK found that they also expressed concerns regarding the loss of education and the wellbeing of their children (Bonell, 2021). The fear of academic failure has been associated with increased anxiety in students (Zhao et al., 2021), and remote learning has had a profound effect on the mindsets of adolescents as well, with a research report by Prince's Trust revealing that 44% of 16–25-year-olds now have lower goals and ambitions for the future. With up to 41% of people now believing their goals are unattainable, the self-esteem of students has decreased (Glasper, 2021). Schools are not only sites of education; they also provide support to their students through counseling. However, school closures have led to a shift from physical counseling to tele-health or eMental Health Services. A study found that students were less likely to reach out for support during this time of remote learning, but those who did received help for longer and spoke about more personal issues (O'Conner, 2020). Matters including adjustment, grief, self-esteem, and identity were spoken about much more frequently during this period of remote learning compared to previous data from 2019 and 2020 (O'Conner, 2020). With more stress and anxiety and less conventional ways of reaching out for help, many of the feelings and concerns that students already had were intensified.

### *Personal Habits*

With new environments and norms, changes to the lifestyles of adolescents are to be expected. A Polish study found that physical activity after school closures decreased significantly and a report by Statista found that screen-time increased in the United States, with

children of all ages spending on average an additional 4 hours on electronic devices. Results from this report were found to be consistent with studies on children and adolescents performed in Spain and China (Luszczki et al., 2021). The study also found that sleep in adolescents decreased by 0.28 hours on average on weekdays, and 0.59 hours on average on weekends (Luszczki et al., 2021). A survey of 7958 Italian parents (only 6210 were included in the results listed) uncovered that 69.3% of families reported that children had a more difficult time falling asleep, with 30.2% of families reporting that children had a harder time remaining asleep, and 18.7% of families reporting an increase in the number of nightmares and night terrors their children had (Dondi et al., 2021). Surveys and studies performed across multiple different countries all came to the same conclusion: the sleep of adolescents was harmed.

### *Relation to Emotional Development of Adolescents*

Schools are an essential part of student socio-emotional health and closures have resulted in parental concerns over their children's mental and emotional wellbeing (Garbe et al., 2020). As a result of this pandemic and new remote environment, parental influence over their children has dramatically increased. Studies that have spanned multiple generations have found that the specific style of parenting used in a household impacts the development of emotional function over time and generations alike (Stack et al., 2010). Parental relationships impact the way that their children express and regulate their emotions, especially during adolescence. A study of adolescents showed that positive parental relationships and the perception of family cohesion were related to more efficacious and successful emotional regulation. Maternal support was found to decrease the emotional symptoms of children such as internalizing of emotions, depression, anxiety, etc. (Morris et al., 2017). The development of the ability for children to regulate their emotions is an important part of

their emotional development. As a child develops, increased regulation of their emotions leads to more social interactions, further affecting their behavioral processes (Thompson, 1991).

With a new remote environment, adolescents have been exposed to more stressors than normal. One of the most prominent issues caused by a remote environment is anxiety, stemming from the fear of falling behind in school, loneliness and isolation, or parental relationships and home environments. Science has shown that exposure to situations that cause consistent fear and anxiety can disrupt the development of the adolescent brain, leading to lifelong consequences on learning, behavior, and health (National Scientific Council on the Developing Child, 2010). Sleep is shown to be a fundamental part of metabolic, immune, cardiovascular, and respiratory functions, as well as cognitive and psychological processes. It affects learning, memory, creativity, emotional memory, stress-coping mechanisms, and cognitive abilities and processes (Brand & Kirov, 2011). As a result of this pandemic, adolescents have been shown to receive less sleep compared to before. Sleep is a vital process, especially during adolescence, a time of growth and development. Factors such as stress and anxiety have been shown to affect sleep (Brand & Kirov, 2011). A study of adolescent rats exposed to stressors revealed that stress can significantly affect the structure and function of the brain, causing problems that can still be experienced during adulthood. It was found that during adolescence, stressors of both the physical and emotional varieties could notably impact the mossy fiber system of the brain, a system that contributes to the pathophysiology of depression, increasing the susceptibility of developing depression (Eiland & Romeo, 2013). The effects of changes in social environments are exacerbated during periods of development, when social interaction is crucial to regular emotional development, and stressors have been

found to severely impact social behaviors (Eiland & Romeo, 2013).

Social interaction is also an integral part of the emotional development of a child, especially during adolescence. A study of mice who were isolated during their period of adolescence found that a deficiency in social interaction affected their brain and behavior, especially during stages of development (Orben et al., 2020). The importance of social interaction and the effects of deficiency were shown in as little as 24 hours, with mice who were isolated showing increased amounts of anxiety and excess activity. A prolonged period of isolation analogous to the quarantining and remote environment students faced resulted in an increase in the aggression and reactivity to stress of the mice (Orben et al., 2020). Isolation during the period of adolescence can result in impaired cognitive flexibility and typical learning behaviors such as reward learning and reversal learning with similar effects and behavioral changes observed in mice who were not isolated as extremely (Orben et al., 2020). Complete social isolation of mice specifically during the period of adolescence resulted in structural and functional changes in their brains, affecting dopamine and serotonin systems and influencing motivation and reward systems (Orben et al., 2020). Dopamine systems have been shown to develop in humans during adolescence and are especially active during this period (Galvan, 2010). Rewards are rarely, if ever, seen during isolation, and a deficiency in social interaction that would cause the development of this system could severely impact the way adolescents experience life as they grow older, as reward systems are responsible for our behavior, motivation, and interactions (Bhanji & Delgado, 2013). Studies in adolescent primates have also been done, revealing that isolation for as little as 1-3 weeks can cause a decrease in the growth of the hippocampus, the part of the brain that is responsible for memory and learning. Studies among other animals of all ages have shown that

social interaction is a universal necessity (Orben et al., 2020). While adolescents in solitary confinement have shown similar symptoms, it is important to note that the social worlds of animals differ greatly from the complexity of human society (Orben et al., 2020). This is not to discount the validity of mice experiments however, as mice and rats are and have been crucial in human biomedical and behavioral research due to their anatomical, physiological, and genetic similarity to humans (Bryda, 2013). While the circumstances may not be as extreme as those of solitary confinement, with most students in the world shifting to an all-remote environment, it is still important to note that a lack of social interaction can take a toll on adolescents and affect them emotionally and mentally in profound ways.

## Discussion

These results show that a remote learning environment can have damaging repercussions on the lives of adolescents. With a combination of familial, social, and personal issues brought on by confinement and school closures, it is important to prevent long-lasting socio-emotional damage that may result from the effects of remote environments on adolescent emotional development. One of the main problems of a remote environment is the feeling of isolation and disconnection. While there are no ways to prevent this, possible strategies to reduce or combat these feelings include maintaining social networks and allowing adolescents to experience social rewards. The sense of belonging both in a family and a community are essential as well as the knowledge that there are people who understand and can provide support. Even so, it is not enough to simply increase the frequency of social interactions. In a period of solitude, it is vital to find a sense of purpose and to discuss negative thoughts (Loades et al., 2020). With social distancing still in effect due to the COVID-19 pandemic, socialization with other people may not always be an available option. Digital programs

based on cognitive-behavioral therapy (CBT) have been developed and have been shown to be effective at alleviating symptoms of trauma such as anxiety. Programs such as BRAVE-TA, MoodGym, and SPARX, have all been shown to have positive effects on emotional health (Loades et al., 2020).

Limitations to this study include the world's unfamiliarity with remote learning environments, as schools are conventionally held in person. While research has shown that isolation can have harmful effects on humans, the situation that we find ourselves in now is unlike any other the world has seen before. The data that has already been revealed has shown that a remote learning environment can cause detriments in the emotional development of adolescents. For that reason, more research should be done about the implications of such a long-term quarantine to better help the future generation of the world.

## Conclusion

To conclude, the onset of a new remote environment as a result of the COVID-19 pandemic has severely impacted the emotional health of adolescents, causing changes and impairments to normal emotional development. With new environments and influences in their lives such as parental stress, social isolation, and online learning, adolescents faced higher levels of stress and anxiety overall, affecting sleep and social interaction, two essential components in development. The circumstances brought on by a remote environment can cause changes in brain structure, function, and development, increasing negative emotions, negative coping mechanisms, and psychological disorders, all of which can have a long-lasting effect on the wellbeing of the adolescent as they progress through adulthood.

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## My Uncle and His Struggle with COPD

Marko Zimic

Stuyvesant High School, United States

mzimic04@gmail.com

### Constricted

As he rounds the corner onto 81st street, the familiar feeling of dread fills his stomach. He parks the family's navy-blue Jeep and braces himself for the worst. He grabs his stuff and opens the door. He grasps the handle above the door and pivots himself in his seat. He begins to lift himself up out of his chair, place his feet on the pavement below, and lower himself completely out of the car. By the time he is done, he is gasping for air, exhausted.

After pausing to catch his breath, he proceeds to the front entrance, unlocking first the glass door and then the wooden one. Behind it, his wife and three children wait inside, the oldest fourteen, the youngest only seven. He steps inside and situates himself. His breathing is heavy, audible, and concerning to a point.

While the kids play in the above-ground pool in the back, he stands by the barbecue, watching the burgers, hot dogs, and vegetables roast above the flames. He flips them every so often, but even something as simple as turning a cob of corn is enough to leave him depleted. If you listen close enough, you can hear faint turbulence every time his chest rises and falls. Aware of his nearly constant panting, his wife approaches from behind, asking him – as always – how he feels, if he needs anything, if there is anything she can do to help.

He finishes cooking dinner, eats, and lowers himself onto the couch, nodding off as he often does; his condition causes sleep apnea, making it nearly impossible to get a decent night's rest, leaving him perpetually exhausted. As his

wife leaves to work the night shift as a nurse at New York Presbyterian and the kids climb into bed, he lifts himself off the couch. As he recalibrates and gains his balance, he suddenly feels sore, lightheaded, and as if he is drowning. By the time he makes it up the flight of stairs linking the living room to the second floor, his chest feels like it is going to implode. Upon entering the master bedroom, he turns on the air conditioner – the cool air soothes him – and pulls the covers over himself, his whole body aching with the strain he felt at work, in the car and on the subway, at home – all day. He turns off the lamp to finally shut his eyes, but before he does, he glances at the gray apparatus lying in the corner across the room. Although he can barely sleep without the CPAP machine, he cannot at all with it. He prays that he makes it through the night safely. The lamp goes out.

This is the reality that my uncle, JZ, lives every day. My uncle suffers from chronic obstructive pulmonary disease (COPD) but to say that his condition is the result simply of general COPD or that his only symptom is difficulty breathing is an injustice to him, to the 15 million other Americans who struggle with COPD, and to the 150,000 Americans who die annually from COPD and its complications.

Chronic obstructive pulmonary disease, also sometimes known as chronic obstructive lung disease (COLD) and chronic obstructive airway disease (COAD), is a type of degenerative lung disease. This means that it progressively worsens over time and exists on a spectrum, from

mild trauma and symptoms to severe, life-threatening conditions. The two most common variants of COPD are emphysema, in which the alveoli are enlarged and their walls are compromised, resulting in permanent lung damage, and chronic bronchitis, in which the bronchi become inflamed and thus constricted. Although the main symptoms of COPD are coughing and shortness of breath, the disease can affect the body in other ways, resulting in other conditions and symptoms, as we will see with my uncle.

Similar to many others with COPD, JZ's case is not the result of one single acute factor – rather, it is the culmination of long-term exposure to many potential risk factors over an extended period of time. First, JZ suffered from asthma long before he was diagnosed with COPD. This means that even from a young age, his lungs were already compromised and hypersensitive to risk factors for COPD and other illnesses. Moving past asthma, the most decisive factor by far in the development of my uncle's COPD is smoking. JZ is part of a very large statistic – it is estimated that 85 to 90 percent of all COPD cases are a result of smoking tobacco and long-term exposure to secondhand smoke. Although he quit in 2017, JZ began smoking in 1996 after taking his first puff at the age of 17 at a rate of about a pack per day, which translates to 25 years' worth of tobacco smoke in his lungs and even more years of exposure to secondhand smoke.

Although the coupling of asthma and smoking is probably the basis from which my uncle's COPD sprouted, proximity to other risk factors certainly accentuated and catalyzed its development. As an ironworker, JZ is often exposed to potentially harmful particulate airborne matter when on job sites and within their vicinities. Moreover, he works almost exclusively in Manhattan, where air pollution levels are significantly higher thanks to constant automotive traffic. Considering the fact that JZ has worked in the ironworking industry for well over twenty years, it is easy to see how exposure to irritating air pollution on a daily basis

could easily have an impact on the development of his COPD, which was diagnosed in 2017, shortly before he quit smoking. To make matters even worse, JZ contracted coronavirus in 2020, causing further lung damage due to prolonged inflammation and autoimmune response.

With regard to the COPD itself, JZ experiences a specific type of ailment called bronchiectasis. Bronchiectasis is similar to emphysema in that the airways become larger in diameter. However, in bronchiectasis, the cough that results from the widened airways causes blood vessels in the walls of the airways to pop. Consequently, the subject experiences hemoptysis – the coughing up of blood – and thick, tough scar tissue forms in the lungs. As a result, the lungs are no longer able to drain normal mucosal secretions and become more vulnerable to infection, which creates nearly constant conditions for inflammation. Thus, the lungs lose function over time.

Although JZ experiences a variety of symptoms, the ones he experiences most often are those most directly related to his COPD. Coughing, dyspnea (difficulty breathing), hemoptysis, and sleep apnea (periodic lapses of breathing while sleeping) are among the most debilitating symptoms he exhibits on a day-to-day basis. However, it is suspected that other health complications of his – and thus, their symptoms – are connected to or even potentially caused by his COPD. An electrocardiogram revealed that the left side of JZ's heart was enlarged. Further examination showed abnormal ventricular relaxation on the left side, which means that his heart's left ventricle pumps irregularly. After wearing a cardiac monitor for a month, it was also found that JZ suffers from non-sustained ventricular tachycardia – in other words, his heart beats at an irregularly fast rate for short periods of time. These are both early indicators of heart failure, meaning JZ has to take extra care when it comes to his activities and his diet.

It is a typical Saturday morning, the sky scattered with high, wispy clouds. As per usual, JZ clambers

out of bed exhausted because he could not fall asleep for more than an hour at a time. He heads downstairs and treats himself to breakfast. He waits for the kids to get ready, helping the youngest one dress into his soccer uniform. Then, they are off.

En route to the soccer game, everything is very normal. Traffic jams and lousy drivers clog the roads. They arrive, and the kids pile out of the car. He follows, much more slowly and deliberately. Again, as he gets up, the pounding in his chest ensues, and it is sustained as he walks across the patchy soccer fields behind the enormous Con Edison plant and dilapidated halal butchery to get to the field on which his boys will be playing. However, while the boys play, his consciousness begins to lapse. Because he is too tired, he cannot resist nodding off no matter how hard he tries. The pseudo-narcolepsy plagues him everywhere – at his sons' soccer games, at work, and while running errands.

After the games, they beg him to stay and kick the ball around with them. As always, he acts hesitant, but both he and the boys know that the answer is always yes. But there's a catch, an unwritten rule. Each and every time the ball goes past his reach, one of the boys has to get it for him. The boys don't think much of it, but it haunts JZ. It pains him immensely that he cannot spend his limited time with his children as he would like. And it is his greatest lament that his boys must see him, their greatest role model, in a position of such helplessness.

This is perhaps what JZ, as well as others with COPD and related illnesses, finds most debilitating about the disease – the impact it has on his relationships with those close to him. In an interview with JZ, he stated that there are two ways to deal with the effects of COPD, the first being to do half the work you normally would, and the second to work twice as hard and do the same amount of work you used to. JZ explains that this affects his productivity and his relationships with those both at work and at home. In the domestic sphere, he is responsible for doing work on the

house (he is in construction, after all) but tends to back away from most other physical things like cleaning, for example. As a result, his wife (who has her own set of debilitating health issues, including herniation) and children assume a good chunk of domestic labor.

JZ also finds that COPD presents obstacles to his productivity at work. In the workplace, JZ is the foreman in his squad of ironworkers. Consequently, he still does a decent amount of physical labor, but not nearly as much as he used to. Regardless, he still feels suffocated whenever he does any hands-on tasks. If JZ were not a foreman, however, he would have to complete much more physical work than he currently does, which of course means he would be subject to even more respiratory strain. Moreover, JZ has a very supportive network of coworkers, who know what sorts of barriers he faces and are always more than ready to assist him when he needs something done.

In retrospect, JZ is quite lucky when it comes to his circumstances, despite his horrible illness. He can find support from his immediate and extended family and from his coworkers, and he can be accommodated if need be. However, he concedes that for others who may not be as fortunate, the case could be radically different. For those who lack supportive family – or any family at all, for that matter – it may be difficult to complete certain tasks around the house, resulting in an overall lower quality of life. It may also be hard or impossible for them to afford domestic assistants or caretakers who could assume some of the responsibilities which COPD makes difficult to complete. For those who do not have supportive networks or are not in positions of power in the workplace but nevertheless have physically demanding jobs, productivity might be greatly reduced, making staying employed or even finding employment difficult in the first place. This being said, those battling COPD – and any illness, in reality – actually often find themselves embarking on two separate expeditions. The first journey is, of course, combatting whichever

illness they unfortunately have. The second, however, is effectively navigating the very mechanism that tries to help them – the healthcare system.

In his experience with the healthcare, JZ has two overarching gripes with the system. The first is lack of comfortable treatment options and lack of patient autonomy. With regard to the treatment options, he is rather unsatisfied with the therapies available. For his bronchiectasis and asthma, there is little he can do but lead a healthier lifestyle and take medicine, respectively. Unfortunately, that is just the nature of his condition, and there are few other treatments available. For his sleep apnea, he had a choice between only two possible treatment options. He quickly became disillusioned with the CPAP machine, the option he ended up with. He finds it incredibly uncomfortable and impossible to sleep with, describing the feeling of exhaling with it as “burning your whole sinuses.” Thus, the machine does nothing but worsen his inability to sleep soundly through the whole night. He also finds maintaining the machine cumbersome and logistically impractical. He thinks the nature of the machine is unnecessarily complex and often struggles to thoroughly clean the device.

When at the specialist for his sleep apnea, he was presented with his two options, the CPAP machine and Inspire sleep apnea therapy, which involves the insertion of a device into the respiratory tract. Although JZ had tried a CPAP machine some years before and was willing to participate in another sleep study for clearance to use the Inspire device, the doctor ultimately overruled his request and put him on the CPAP machine again even though JZ would have met all the criteria necessary to use the Inspire device. JZ was disappointed with this outcome, and in his eyes, rightfully so. JZ acknowledges that doctors are trying to help, but he believes that patients should have the final say in how they want to be treated. After all, it is the patient who suffers from their illness – not the doctor. However, despite his issues with his treatment, JZ understands that

developing effective, safe, and efficient treatments for any illness requires years upon years of research and immense monetary and human resources. In that vein, he hopes that in the future, more treatment options for COPD and other common illnesses will be developed that are more comfortable and logistically simpler. He also hopes that patients will be awarded more autonomy when it comes to picking treatment options.

JZ’s second issue with healthcare is lack of availability on part of the doctors. Because JZ has many conditions beyond COPD, including those aforementioned heart problems as well as hypertension, he goes to see specialists quite often. When making appointments, one thing he notices is that doctors are very rarely available. For example, he is still waiting to book an appointment with a stroke specialist he was referred to after reporting a case of vision loss in well over six months ago. There are very few vacant time slots which anyone seeking help can book, making it hard to receive medical assistance. Although this issue has certainly been exacerbated by the recent coronavirus pandemic, it is really part of a wider, much older trend; over the past two decades, the number of physicians in the United States has been shrinking, even as the population as a whole has been increasing. By 2033, it is estimated that the United States will have a shortage of as many as 139,000 physicians, meaning that it will be even harder for people to receive medical help of any sort. This is an incredibly significant statistic that those in medicine need to be aware of. Does more need to be done to encourage young people to pursue medicine as a career? Should the financial barriers to a medical degree be reevaluated in order to get the most talented and dedicated individuals into the industry?

Moreover, JZ notes that the geographic distribution of doctors is widely skewed. Even though he lives in Queens, New York, an area that is somewhere between urban and suburban, he frequently has to commute for more than an hour

each way to see any specialist, as most of them are concentrated in wealthier but less populated Manhattan. For people who live in areas further from places with high concentrations of doctors, seeing a physician who may save their life may be beyond difficult. It is for this reason that JZ hopes one day the medical community will integrate more fully into areas lacking specialty medical care to tend to those whose geography may be a fatal disadvantage.

As of now, JZ's future is uncertain. He will sadly struggle with the consequences of COPD and other complications for the foreseeable future, which leaves his health up in the air. COPD is not curable, but it is treatable and preventable. There is much that can be done to increase awareness around prevention to lower communities' risks of developing respiratory issues. Abstaining from smoking tobacco or other substances and minimizing exposure to air pollution and harmful particulates takes care of the most prominent risk factors. In the future, it is critical that we listen to patient experiences like JZ's and try to incorporate feedback when we can to improve the healthcare system and to make it more equitable, accessible, and convenient for those that use it.

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