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Alzheimer's Disease: Risk and Protective Factors to Improve Detection and Prevention

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This is to certify that the doctoral dissertation by

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Walden University
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Abstract

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MS, University of Southern California, 2016

BS, University of Washington, 2012

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

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Abstract

Alzheimer's disease (AD) is a growing epidemic and is the sixth-leading cause of death in the United States. Individuals with AD often have comorbidities due to the aging process. There is a lack of research on comorbidities as associated risk factors for AD. The leading hypothesis indicates that cardiovascular health issues, environmental exposure, social isolation, and amyloid-beta plaques influence cognitive health and are associated with AD. This study, guided by Finch and Kulminski's AD exposome, is a caveat to explore a patient's physical history of cardiovascular health, modifiable behavior, social isolation, and an AD diagnosis. Participants provided health information collected in the National Alzheimer's Coordinating Center Uniform Data Set. A random selection of (n = 1,229) participants was selected for each manuscript. Bivariate linear regressions identified the association between independent variables and an AD diagnosis. The models found significance between modifiable behavior, social isolation, and the presence of amyloid-beta plaques and an AD diagnosis. There were limited significant correlations between individual variables other than the presence of amyloid-beta plaques, alcohol use, and participant level of independence. Future research needs to identify the association between additional variables to improve understanding of the heart-brain/social connection and the presence of amyloid-beta plaques and AD diagnosis. Understanding these connections could improve health care providers' ability to detect AD earlier and improve therapies and patients' quality of life, contributing to positive social change.

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Dedication

To my family, thank you for all of your love and support. Your encouragement and enthusiasm for education have provided me with the strength needed to complete this task. Lastly, the inspiration for this research comes from the loss of my great grandfather, who lost the battle with Alzheimer's Disease. I am sure your garden in heaven looks amazing!

To my friend and colleague, Holly. We have gone on this journey from the day we met at our first residency. You have been one of my biggest supporters and always there for me. You are my unicorn!

Lastly, to my husband, Mike, I would not have been able to do this without you. You have supported me through my academic journey and always encouraged me to reach my goals and dreams. You are my best friend, and there are not enough words to explain how much you have done for me during this process.

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Dr. Daniel Lee, thank you for being a member of my committee. Your guidance and advice have made me a better researcher and thinker. I appreciate the level of detail you have opened my eyes to and your passion for data analysis.

Dr. Simone Salandy, my university reviewer. Thank you for your feedback and guidance. I am grateful that you were on my committee and for all of your help.

Lastly, thank you, Dr. Steve Tippins. You were and are the most excellent dissertation and life coach. Your encouragement and much-needed advice are why this dissertation is in existence.

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Part 1: Overview

Introduction

Alzheimer's disease (AD) is a major neurological disorder that adversely affects health outcomes such as mental and physical capabilities, quality of life, and life expectancy. AD is the most common cause of dementia and affects more than 6 million Americans over 65 years, with symptoms generally occurring during a person's mid-60s (National Institute on Ageing [NIH], 2017). According to the Centers for Disease Control and Prevention (CDC, 2020), AD is the sixth-leading cause of death in the United States, with diagnoses expected to triple by 2060 to over 14 million people. Consequently, AD's current and future problems beyond the individual level include excessive burdens on families, communities, and societies. Although there is no current cure for AD, medical treatment and early intervention are vital for improving individuals' lives afflicted by AD and their caregivers (CDC, 2020). Decreasing the adverse effects of AD is a challenge that requires early detection and intervention by identifying fundamental variable interrelations and promotion of prevention.

Although increasing age is the leading risk factor for AD, numerous research studies include additional variables contributing to the disease, including heart health, behavior, and an individual's environment. Recently, studies have focused on, and found, associations between such variables and risk factors for heart disease and stroke that increase AD risk (Finch & Kulminski, 2019). For example, Stakos et al. (2020) indicated a connection between amyloid-beta (Aβ) peptides, cardiovascular disease (CVD), and AD at the individual level. Additional studies find that long-term environmental

exposure, modifiable factors, and location are associated with cardiac health and AD (Bagheri et al., 2018; Eid et al., 2019). These studies encourage additional investigational research that explores individual and collective associations between heart health, environmental/behavioral risk factors, and AD to improve health outcomes.

The concept of neurocognitive decline due to the degenerative disorder (i.e., AD) in numerous studies and clinical trials over the last 25 years hypothesizes correlations between Aβ, known to cause cell death in the brain. Reducing the Aβ load is associated with decreased synaptic loss and increases in memory retention, known as the amyloid cascade hypothesis (Ricciarelli & Fedele, 2017). However, a growing body of research opposes the hypothesis as the main factor of AD etiology. Ricciarelli and Fedele (2017) contest that although Aβ plaques and tau neurofibrillary tangles may exist in a patient, not all accumulations of Aβ and tau show signs of cognitive decline.

Current research regarding cardiovascular health, environmental/behavioral risks, and AD mechanisms needs exploration. There may be more to the etiology of AD beyond Aβ plaques and tau tangles based on environmental factors (Finch & Kulminski, 2019). The three independent studies in this manuscript explore participants' history of cardiovascular issues, substance abuse (i.e., smoking and alcohol use), and psychological connectedness data to improve the identification of individuals and communities at risk for AD due to modifiable and nonmodifiable factors (e.g., amyloid plaque and tau abnormalities, CVD, demographics, and environment). In this research, I intend to fill research literature gaps by explicitly addressing early AD detection and intervention

development with data from a uniquely defined cohort of participants across the United States.

Problem Statement

The situation and issues that prompted me to search the literature stem from the health outcomes of longer lifespans and social determinants of health that people's quality of life at the individual and societal levels, risk and protective factors associated with AD, and the creation of interventions to decreasing morbidity. People live longer at an increased risk of developing AD, a cognitive disease that currently has no cure (CDC, 2020). Stakos et al. (2020) and Finch and Kulminski (2019) indicated numerous hypothesized risks for AD beyond aging that need investigation to promote early detection and intervention to decrease the adverse effects of AD.

For all three manuscripts, I analyzed data collected by the National Alzheimer's Coordinating Center [NACC] to identify the level of association between AD diagnosis and exposure to cardiovascular health issues, environmental exposure, and social isolation. Although researchers have investigated these issues, the topic has not been explored by selecting a single cohort to identify a level of association between three major risk factors. The specific research problem to be addressed is identifying the level of influence cardiovascular, environmental, and social risk factors have on AD diagnosis.

Purpose

The three manuscripts aim to examine the level of influence hypothesized social determinants of health and disease/comorbidities have on patients diagnosed with AD. Secondary data includes prospective, standardized, and longitudinal clinical evaluations.

This project is unique as it integrates modifiable and nonmodifiable factors with hypothesized links to AD (Eid et al., 2019). The participants are from across the United States, with data collected between 2005 and 2020 (National Alzheimer's Coordinating Center [NACC], 2021). Additionally, the study's uniqueness supports the union of randomized participants within a secondary data set and the selection of variables associated with cardiovascular health and environmental/behavioral risk factors.

Background

Numerous studies, hypotheses, and theories explore and identify the causes associated with the onset and diagnosis of AD. An individual's health history, modifiable behavioral health risks, and environment contribute variably to AD risk (Finch & Kulminski, 2019). Studies contributing to creating the three manuscripts include cardiovascular health indicators, behavioral risk, and psychological issues associated with environmental conditions (e.g., personal care and mental engagement). The presence of Aβ plaques and tau tangles, cognitive decline, and AD diagnosis are commonalities with each manuscript's three main topics. There is a need to evaluate them independently within the same sample cohort to identify potential levels of association. Finch and Kulminski (2019) indicated that modifiable risk factors and early detection based on a person's health would improve interventions that promote longevity and decrease the adverse effects of cognitive decline. The gap in the literature, which is evaluated, is identifying the level of impact cardiovascular health indicators, behavioral risk, and psychological issues have on a group of participants who have participated in a cohort study across the United States and equally evaluated over a similar period. The unique

nature of this evaluation is identifying a constant seen within a small cohort that suggests interventions beneficial to the larger population to decrease the burden of AD. The following literature review explores the primary hypotheses and concepts related to three risk factors that contribute to the onset and diagnosis of AD and aid in identifying further research that promotes the rationality and methodology for each manuscript.

Literature Review

A large body of evidence from AD studies correlates cardiovascular and behavioral risk factors with cognitive decline. Dementia, in many forms, includes cellular and molecular mechanisms similar to CVD, such as atherosclerosis, characterized as a build-up of plaque in artery walls (Stakos et al., 2020). The shared biological process of aging, CVD, and AD types of dementia share many commonalities. Tini et al. (2020) explained that aging increases the prevalence of AD and CVD, and both have similar underlying mechanisms and risk factors. The authors conducted a narrative review that examined AD and CVD risk factors based on criteria that include community-based studies, diagnostic standardization, the raw prevalence of data, and discrete age and gender reporting (Tini et al., 2020). They hypothesized a “head-to-heart” link based on brain vascularization and its consumption of oxygen-dependent on cardiovascular function. Hypoperfusion occurs in the brain if the heart fails to provide optimal oxygen output, contributing to Aβ plaques, tau tangles, acidosis, and oxidative stress.

Cardiovascular risk factors associated with AD also contribute to the breakdown of the blood-brain barrier, impairing the clearance of Aβ found in the brain and the heart (Tini et al., 2020). Other than age, there are indications that risk factors such as

hypertension in mid-life and high total cholesterol are strongly correlated with CVD and AD (Troncone et al., 2016). They also indicated that modifiable risk factors (e.g., physical activity, health behavior, higher education, and current cognitive activity) are environmental and associated with AD prevention. Additionally, gender differences indicate that women are at greater risk of AD, especially if they have experienced heart failure (H.F.). Tini et al. (2020) contended that more population-based studies need to examine cardiovascular risks to identify preventative interventions and early detection of AD.

Another risk factor associated with AD is long-term substance abuse. Cigarette smoking and alcohol use are two of the most prevalent and easily accessible substances associated with AD. Larsson et al. (2017) found that the odds of AD diagnosis correlate with modifiable behaviors, including cigarette smoking and alcohol use. The authors applied a Mendelian randomization approach to assessing the association between modifiable risk factors with a Bonferroni corrected significance level of 0.05. The researchers indicated a direct positive correlation between the number of cigarettes smoked, the amount of alcohol regularly consumed, and the risk of AD. The authors suggested that more research is needed to determine the pathways associated with the behavioral risk factors (e.g., presence of Aβ plaques and tau tangles) to build on the research gaps and create educational interventions.

Chronic alcohol use and smoking is a more recent study that indicates an increased risk for AD via neurological degradation and impaired cognitive function disrupting nerve signals in the brain (Langballe et al., 2015). Peng et al. (2020) conducted

an epidemiological literature review. In human and mice trials, they found that alcohol and exposure to cigarette smoke increase the presence of Aβ plaques and tau tangles and increase the odds and progression of AD and cognitive decline. Additionally, Durazzo et al. (2018) found that cigarette smoke independently contributes to adverse brain atrophy and AD onset via the thinning of cortices. Both studies indicate that modifiable behavioral risk factors play a significant role in AD diagnosis and suggest the need for more research to determine the impact of heavy alcohol use and smoking (i.e., the most common and avoidable substance).

A person's physical health (e.g., past cardiovascular issues) and modifiable behavior are two factors that may contribute to AD. However, there is increasing evidence of a trifecta between physical health, behavior, and psychological welfare. Living situations, personal care, and engagement with one's community profoundly affect neurological and cognitive health.

Salinas et al. (2021) assessed social support in a cohort study of participants 45 years and older to identify the impacts of loneliness and isolation and the presence of dementia and AD. The authors found a significant association between a lack of social support and lower cognitive function. Living in isolation, lower listener availability, and social interaction's overall presence/availability are vital to mental and cognitive health.

Social interaction, such as a person's living situation (e.g., living with a spouse), level of independence, and type of residence, have varying effects on AD health outcomes. Seaman (2018) explained the negative influences of not receiving care pre and post-AD diagnosis. The author conducted a 26-month ethnographic study of participants

with early onset of AD, their families, and healthcare providers. Through qualitative analysis, Seaman (2018) found that participants who had regular interactions with family and lived in social environments that supported conversation and engaging activities were much better than those in isolation or living in care facilities that did not promote regular engagement. This research promotes the need for an analysis of living situations, level of independence, and a person's type of residence to identify potential risk factors associated with AD diagnoses, such as the presence of Aβ plaques and tau tangles. Bagheri (2018) additionally indicated a need to use spatial analysis and clustering to identify populations where isolative living situations occur to improve interventions that promote interaction for communities at risk for AD based on available demographic and census data.

Theoretical Framework

This study's theoretical framework combines Bronfenbrenner's (1977) ecological systems theory and Finch and Kulminski's (2019) AD exposome. The ecological systems theory provides a framework that explains the complex system concerning a person's environment and individual development. The approach offers a holistic approach to understanding the nature of a person's environment and potential risk factors for developing AD. The AD exposome adds to Bronfenbrenner's model by specifically theorizing a need to evaluate environmental factors associated with genetic and nongenetic risks for AD. The two theories work in concert to offer guidance on approaching AD research gaps while providing insight into the challenges associated with multilevel analysis.

The concept of comorbidity and environmental exposure concerning AD risk and diagnosis includes numerous hypotheses and variables. The three manuscripts apply a combination of Finch and Kulminski's (2019) AD Exposome as a caveat to explore patients' physical history of cardiovascular health and environmental exposure to modifiable risk factors (i.e., alcohol and tobacco use) and Bronfenbrenner's (1977) ecological systems theory to build on the social determinants of health associated with social interaction and cognitive decline. Both theoretical frameworks work in concert to aid in researching potential links between a person's history of cardiovascular issues, smoking and alcohol use, and psychological connectedness data and associations with Aβ plaques and tau tangle biomarkers associated with the early onset and diagnosis of AD.

There is no clear understanding of environmental and modifiable risk behaviors concerning the early onset of AD and cognitive decline. Finch and Kulminski (2019) explained individual differences in environmental exposure to AD risk factors beyond aging and AD-genetic risk. They suggested that brain aging and cognitive decline are vulnerable to multiple variables. Their theoretical framework proposes the 'AD Exposome' to identify modifiable risk factors related to AD development, both endogenous and exogenous. They proposed the need for more research focusing on extraneous factors beyond genetics to provide a more holistic understanding of AD risk. Exogenous exposure, such as carcinogens associated with smoking and alcohol use and endogenous risks (e.g., cardiovascular issues and obesity), are known to influence the presence of Aβ plaques biomarkers associated with AD (Finch & Kulminski, 2019). The extent of such modifiable risk factors is in question, provoking a need to research both

endogenous and exogenous variables associated most strongly in current medical and sociological findings.

An individual's surroundings and environment include social structures, and engagement with other humans uniquely affects cognitive health. Social support and community engagement (e.g., living situations and access to public facilities) impact a person's risk factors for AD diagnosis and progression (Salinas, 2021). The theoretical framework of ecological systems theory proposed by Bronfenbrenner (1977) explains that a child's microsystem (e.g., health services, family, and peers) plays an integral role in the development and health outcomes, either positive or negative. A person's ecosystem and macrosystem contribute to cognitive health. They include social services/healthcare, attitudes and ideologies surrounding cognitive health decline, and how best to create interventions or care for those within our society (Bronfenbrenner, 1977). The ecological systems theory framework applies in the proposed manuscripts to connect a person's surroundings with AD and risk factors. Cardiovascular issues, smoking and alcohol use, and psychological connectedness all pertain to varying capacities of an individual's microsystems, ecosystems, and macrosystems. Bagheri (2018) indicated that sociospatial variables continuously influence how we live and impact social determinants of health and health outcomes. Similar to a child's development and health outcomes, the ecological systems theory aids in identifying risk factors such as isolation and loneliness with the presence of AD and aids as an indicator to identify Aβ plaques and tau tangle biomarkers.

Overview of the Manuscripts

Healthcare professionals, families, and individuals have struggled to identify the root cause of a person's cognitive decline and AD prognosis. One suggested path to identifying AD risk factors is creating models to investigate participants' behavior, lifestyle, and physical history in cohort data (Nguyen, 2018). AD is a global health crisis, and there are numerous studies and pharmaceutical endeavors targeted at detection and prevention. The traditional pedagogies of AD research, patient care, and standard practices have identified old age as a primary cause of AD. However, novel research, technological advancements, and educational paradigms improve the nature of AD research, resulting in studying the disease via databases and cohort studies from not in-situ (Muirhead, 2019). The vast amount of data collected by healthcare facilities focused on AD research has created a need to create models and investigate modifiable and nonmodifiable risk factors.

This three-manuscript dissertation aims to identify the level of effect three most common risk factors in AD literature (i.e., biological, behavioral, and psychological): the three manuscripts parallel current and past research to address AD disparities. The focus is on improving strategies that identify AD risk factors in a cohort and promoting lifestyle changes throughout communities. Additionally, there is an emphasis on increasing risk factor education and filling gaps regarding the possible level of influence individual social and environmental risk factors have on AD's early onset, diagnosis, and progression.

Manuscript 1

Research is needed to promote public health and identify health history as a potential risk factor for AD for the general community, healthcare providers, and those living with AD. The brain-heart interaction concept needs exploration and its relationship with Aβ plaques and tau tangle biomarkers (Chen, 2021). There is limited research on the level of interaction between past cardiovascular events and issues related to AD. The first manuscript examines patients' cardiovascular physical health, the presence of Aβ plaques and tau tangle, and demographics directed at modeling the levels of correlation via statistical analysis of a primary dataset.

Research Question

Research Question: Based on the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), what are the association levels between past cardiovascular events, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants who are between the ages of 55 and 80 years of age controlling for age and other confounders?

$H_0$1: Based on the NACC Uniform Data Set, there are no associations between cardiovascular health, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

H_a1: Based on the NACC Uniform Data Set, there are associations between cardiovascular health, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

Nature of the Study

The study's nature is quantitative with a cross-sectional design to understand the associations between cardiovascular health and genetic factors associated with AD in participants who provide information to the NACC. The primary reason for forming this doctoral study is to create new knowledge by examining statistical evidence and identifying gaps in the literature. The model applies a bivariate logistic regression with yes or no outcomes and levels of association. This study takes a unique approach as it focuses on a specific population and integrates variables provided by participants indicating a need for further investigation in the literature. The quantitative analysis should identify links between cardiovascular health, amyloid-β plaques/tau proteins, and AD diagnosis.

Limitations, Challenges, and Barriers

The method and research design include a request from the NACC to acknowledge the use of their data. The request was particularly interesting to the IRB as this aligns with consistency and precaution. The IRB indicates that once a proposal demonstrates data confidentiality, informed consent, no conflict of interest, minimization of risk, and documentation between all stakeholders, which is considered an expedited review (Walden University, n.d.a.). I worked with the NACC and my Chair to ensure the completion of expectations from all stakeholders (e.g., properly incorporating the data sources and integrating acknowledgment and gratitude).

Manuscript 2

Research is needed to promote public health and identify modifiable behavior as a potential risk factor for AD, the general community, healthcare providers, and those

living with AD. Substance abuse, specifically the most common alcohol and smoking in the United States, are modifiable risk factors associated with AD (Chen et al., 2021). There is limited research on the level of interaction between past and current alcohol and tobacco use and issues related to AD. The examination of patients' substance abuse behavior, presence of Aβ plaques and tau tangle, and demographics is the subject of the second manuscript directed at modeling the levels of correlation via statistical analysis of a primary dataset.

Research Question

Research Question: Based on the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), what are the association levels between alcohol, cigarette, and anxiolytic-hypnotics use, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants who are between the ages of 55 and 80 years of age controlling for age and other confounders?

$H_0$1: Based on the NACC Uniform Data Set, there are no associations between alcohol, cigarette, and anxiolytic-hypnotics use, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

H_a1: Based on the NACC Uniform Data Set, there are associations between alcohol, cigarette, and anxiolytic-hypnotics use, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

Nature of the Study

The study's nature is quantitative with a cross-sectional design to understand the associations between Aβ plaques and tau tangle biomarkers and modifiable behavioral

factors (i.e., tobacco and alcohol use) associated with AD of participants who provide information to the NACC. This study takes a unique approach as it focuses on a specific population and integrates variables provided by participants indicating a need for further investigation in the literature. The study includes exposure level analysis (e.g., number of cigarettes smoked and daily alcohol consumption).

Limitations, Challenges, and Barriers

The method and research design included a request from the NACC to acknowledge the use of their data. The request was particularly interesting to the IRB as this aligns with consistency and precaution. The IRB indicates that once a proposal demonstrates data confidentiality, informed consent, no conflict of interest, minimization of risk, and documentation between all stakeholders, which is considered an expedited review (Walden University, n.d.a.). I worked with the NACC and my Chair to ensure the completion of expectations from all stakeholders (e.g., properly incorporating the data sources and integrating acknowledgment and gratitude).

Manuscript 3

Salinas (2021) and Seaman (2018) identified social isolation and a lack of community engagement as a conduit of AD's presence and early onset. Research is needed to promote public health and identify participants' social engagement and lifestyle levels as potential risk factors for AD in the general community. There is limited research on levels of interaction between past and current lifestyle issues such as living with others, having a spouse, and available social services use related to AD. The examination of participants' living situation and social engagement, presence of Aβ

plaques and tau tangle, and demographics is the subject of the third manuscript directed at modeling the levels of correlation via statistical analysis of a primary dataset.

Research Question

Research Question: Based on the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), what are the association levels between staying at home rather than doing new activities, dropping activities and interests, and type of residence, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants who are between the ages of 55 and 80 years of age controlling for age and other confounders?

$H_0$1: Based on the NACC Uniform Data Set, there are no associations between staying at home rather than doing new activities, dropping activities and interests, type of residence, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

H_a1: Based on the NACC Uniform Data Set, there are associations between staying at home rather than doing new activities, dropping activities and interests, type of residence, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

Nature of the Study

The study is quantitative with a cross-sectional design to understand the associations between participants' living situations, social engagement, and locational risk associated with AD patients' mortality in the CDC's database. This study takes a unique approach as it focuses on specific social interactions and integrates variables

provided by participants indicating a need for further investigation in the literature. The quantitative analysis aims to identify specific links between living situations, social engagement, and isolation.

Limitations, Challenges, and Barriers

The challenges associated with this study included using secondary data and identifying locations' associations between variables. This study looked at data from states where NACC clinics collect data. However, individuals' locations were de-identified. Rates of mortality provide information about the severity of AD in each state. There were limitations when relating risk factors associated with cardiovascular health and AD mortality.

Significance

This study may provide original statistical data and quantitative analysis that promotes a multidisciplinary approach to AD research. Insights from this study intend to help researchers and health practitioners identify modifiable and non-modifiable risk factors associated with AD and encourage novel interventions. The primary goal is to increase AD prevention and early detection to improve people's quality of life and decrease individual, family, community, and societal challenges associated with AD's economic and emotional anguish. Due to AD's expected growth rates locally and globally, supporting research that successfully aids communities through affordable and accessible prevention and early detection strategies is paramount. Nguyen et al. (2018) conducted a systematic search and review of health care needs and economics associated with AD. The authors indicate that current methods reported for AD treatment are

primarily pharmaceuticals. They propose pivots toward AD and dementia prevention and non-pharmacological interventions, especially in early-onset detection or genetic predisposition.

Significance to Discipline

People in the United States generally live longer through technology, equity, and health care improvements. AD is associated with age, so identifying prevention methods and fundamental risk factors is critical to managing expected increases in the disease over the next 40 years (Finch et al., 2019). Mounting evidence supports AD and health education to inform people of the benefits of early AD prevention through behavioral change and environmental exposure awareness—understanding modifiable risk factors such as genetic, environmental, and lifestyle aids in limiting exposure to AD-associated factors by bringing awareness to social determinants of health (Eid et al., 2019). Additionally, identifying AD-associated risk factors aids in AD research and provides vital information at academic and professional healthcare levels.

Significance to Social Change

Identifying risk factors and promoting early detection/intervention practices work in concert to decrease adverse health outcomes associated with AD to strengthen the case for increased research and outreach, especially in vulnerable communities, to promote positive social change. The concept of changing behavior to promote healthy longevity impacts individuals and encourages social well-being by lessening the burden of AD on families, communities, and health resources (Nguyen et al., 2018). The looming potential for AD development and diagnosis increases as individuals live longer, encouraging the

need to identify the social determinants of health associated with AD morbidity (Muirhead et al., 2019). A more inclusive understanding of AD risk and modifiable behavioral practices promotes positive social change by altering the disease's progression and decreasing its economic and social burden.

Summary

As people in the United States live longer, there is a need to identify AD-associated risk factors to promote interventions that prevent AD progression through early detection, modifiable behaviors, and environmental exposure. Currently, known risk factors for AD are associated with Aβ plaques and tau tangles, and numerous variables contribute to their presence as people age (Pascoal et al., 2017). An individual's health history, modifiable behavioral health risks, and environment contribute variably to AD risk (Finch & Kulminski, 2019). Selecting principal risk factors associated with the presence of Aβ plaques and tau tangles and AD provides a framework that supports past and current research by identifying levels of association. Cardiovascular health, substance abuse, and a person's social engagement all work in concert at varying levels via the presence and progression of AD (Stakos et al., 2020; Xue et al., 2017). Identifying levels of risk to create a comprehensive approach to improve interventions as people age is key to decreasing the burden of AD as populations live longer.

Although researchers have investigated the associations between an individual's health history, modifiable behavioral health risks, and environment, limited uniform studies apply models that incorporate a cohort of participants across the United States. The National Alzheimer's Coordinating Center (NACC) started collecting in 2005, and

the potential to create unique models to study cognitive decline is vast (Dodge et al., 2020). Before individuals, communities, and healthcare providers can fully understand what interventions best promote risk factor avoidance, there is a need for more comprehensive studies that look at levels of influence based on specific variables. The findings from this three-manuscript dissertation aim to influence society's attitudes toward modifiable behavioral and environmental risk factors and decrease the challenges associated with understanding AD causes.

Part 2: Manuscripts

Facilities of the Heart-Brain Interaction and Alzheimer's Disease

by

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Outlet for Manuscript

Primary Healthcare Providers and Cognitive Researchers: This scholarly, peer-reviewed journal with a targeted audience of primary healthcare providers and cognitive researchers in academia or other settings focuses on topics related to Alzheimer's Disease, including cardiovascular health and the presence of Aβ plaques and tau tangles evaluation. Original research, quantitative database analysis, and statistical analysis are accepted types of manuscripts. Submission guidelines for the *Alzheimer's & Dementia: Translational Research & Clinical Interventions* (TRCI), a peer-reviewed, open-access journal of the Alzheimer's Association, follow.

Research articles cover hypothesis-driven research or evidence-based validation studies. Manuscripts must include: (a) structured abstract, (b) background, (c) methods, (d) results, (e) discussion, (f) references, (g) acknowledgements/conflicts/funding sources, and (h) keywords. Research articles must include a structured abstract, using the IMRAD format (specifically, INTRODUCTION, METHODS, RESULTS, DISCUSSION, using all uppercase letters followed by a colon and space), not exceeding 300 words. Length may not exceed 3,500 words (excluding the abstract, references, figures, and tables), a maximum of 50 references, and no more than six figures, boxes, or tables. All research articles must include a "Research in Context" section. Submission Guidelines for the Journal of the Alzheimer's Association:

- https://alzjournals.onlinelibrary.wiley.com/hub/journal/23528737/homepage/author-guidelines

Abstract

Alzheimer's disease (AD) is a growing epidemic and is the sixth-leading cause of death in the United States. Individuals with AD often have comorbidities due to the aging process. There is a lack of research related to understanding comorbidities as associated risk factors for AD. One of the leading hypotheses is the heart-brain connection, and the presence of amyloid-beta plaques influences cognitive health and is associated with AD. This study is guided by Finch and Kulminski's (2019) AD Exposome as a caveat to explore a patient's physical history of cardiovascular health and an AD diagnosis. Participants provided health information collected in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). The data included questions about the participant's current cognitive health status, including an AD diagnosis, and current and past physical health questions. A random selection of (n = 1,229) participants included (n = 602) not diagnosed with AD and (n = 627) who were diagnosed with AD. A bivariate linear regression was conducted to identify the level of association between cardiovascular health variables and an AD diagnosis. The overall model found significance between the cardiovascular health variables, including the presence of amyloid-beta plaques and an AD diagnosis. The were no significant correlations between individual cardiovascular health variables other than the presence of amyloid-beta plaques. Future research is needed to identify the association between additional cardiovascular variables to improve understanding of the heart-brain connection. Understanding the heart-brain connection could improve health care providers' ability to detect AD earlier and improve therapies and patients' quality of life.

Introduction

Alzheimer's disease is a growing epidemic and is the sixth-leading cause of death in the U.S., with diagnoses expected to triple by 2060 to over 14 million people. Individuals with AD often have comorbidities due to the aging process. Researchers have indicated strong correlations between having comorbidities and the onset/diagnosis of AD (Jørgensen et al., 2020). In the mid-twentieth century, coronary heart disease became the leading cause of mortality in the United States and is a risk factor for heart attacks, strokes, heart valve complications, and numerous other causes of mortality (Ferrucci & Fabbri, 2018). There is a lack of understanding of how brain-heart interaction may lead to an AD diagnosis. Individual cardiovascular-related events may have varying effects on the presence of Aβ plaques, tau tangle biomarkers, and an AD diagnosis (Chen, 2017). The limited research on the level of interaction between past cardiovascular events and issues related to AD requires quantitative exploitation.

Significance

This study provides original statistical data and quantitative analysis that promotes a physiological approach to AD research by assessing the relationship between cardiovascular health and an AD diagnosis. Insights from this study intend to help researchers and health practitioners identify modifiable and non-modifiable risk factors associated with AD and encourage novel interventions. The primary goal is to increase AD prevention and early detection to improve people's quality of life and decrease individual, family, community, and societal challenges. Cardiovascular disease (CVD) is a known risk factor for early cognitive decline and the build-up of amyloid-beta (Aβ)

plaques in the brain (Stakos, 2020). However, current pedagogies fail to address the specific level of relationship between past cardiovascular (CV) events and the presence of AD and Aβ deposits.

This study's theoretical framework combines Bronfenbrenner's (1977) ecological systems theory and Finch and Kulminski's (2019) AD exposome. The principles of the two frameworks apply a combination of Finch and Kulminski's (2019) AD exposome as a caveat to explore a patient's physical history of cardiovascular health and an AD diagnosis. Bronfenbrenner's (1977) ecological systems theory builds on the social determinants of health associated with cognitive decline and a person's environment as potential risk factors for developing AD. Both theoretical frameworks work in concert to aid in researching potential links between a person's history of cardiovascular health data and associations with Aβ plaques and tau tangle biomarkers associated with AD's early onset and diagnosis.

There is no clear understanding of the level of CV risk concerning the early onset of AD and cognitive decline. Finch and Kulminski (2019) explain individual differences in health history and environmental exposure to AD risk factors beyond aging and AD-genetic risk and suggest that brain aging and cognitive decline are vulnerable to multiple variables. Their theoretical framework proposes the 'AD Exposome' to identify modifiable risk factors related to AD development, both endogenous and exogenous. They propose the need for more research focusing on extraneous factors beyond genetics to provide a more holistic understanding of AD risk. Modifiable risk factors include exogenous recognition that CV issues influence AD diagnosis, and endogenous

occurrences (e.g., heart attacks and strokes) promote the presence of Aβ plaques biomarkers associated with AD (Finch & Kulminski, 2019). The extent of such modifiable risk factors is in question, provoking a need to research endogenous levels associated most strongly with AD diagnosis to determine the benefits of exogenous CV interventions.

Relevant Scholarship

Numerous studies have found correlations between cardiovascular health risk factors and cognitive decline as individuals age. Dementia, in many forms, includes cellular and molecular mechanisms similar to CVD, such as atherosclerosis, characterized as a build-up of plaque in artery walls (Stakos et al., 2020). Aging increases the prevalence of AD and CVD, and both have similar underlying mechanisms and risk factors (Tini et al., 2020). Research indicates a “head-to-heart” link based on brain vascularization and its consumption of oxygen-dependent on cardiovascular function. Hypoperfusion occurs in the brain if the heart fails to provide optimal oxygen output, contributing to Aβ plaques, tau tangles, acidosis, and oxidative stress (Tini et al., 2020).

Lourenco et al. (2018) indicate that cognitive impairment and abilities are associated with cardiovascular risks in senior citizens. The study included 33,580 participants over 50 with a mean age of 65.4, and 56.4% were female. The authors reported strong correlations between lower performance in perceived memory, verbal fluency, numeracy, and comorbidities, including prior heart attack, hypertension, and stroke. A stroke was the most prevalent risk factor for cognitive impairment risk. Lourenco et al. (2018) also found that having a myocardial infarction doubled the risk of

cognitive decline for women over 65 years of age. The authors state that their study includes 16 European countries and suggest additional variables need evaluation to analyze the relationship between cognitive decline and cardiovascular risk factors.

Cardiovascular risk factors associated with AD contribute to the blood-brain barrier's breakdown, impair the clearance of Aβ found in the brain and the heart, and are known to be associated with an AD diagnosis (Tini et al., 2020). Other than age, there are indications that risk factors such as hypertension in mid-life and high total cholesterol are strongly correlated with CVD and AD (Troncone et al., 2016). Like Lourenco et al. (2018), gender differences indicate that women are at greater risk of AD, especially if they have experienced cardiovascular issues. Tini et al. (2020) also indicated that modifiable risk factors (e.g., health behavior) are associated with AD prevention. The authors suggest that more population-based studies need to examine cardiovascular risks to identify preventative interventions and early detection of AD.

There is limited research on the interaction between past cardiovascular events and AD-related issues. Chen et al. (2017) indicated that cardiac injuries are a risk factor for cerebrovascular diseases. This group of conditions restricts blood flow to the brain, commonly found in patients after a stroke. The authors add that research is needed to promote public health and identify health history as a potential risk factor for AD for the general community, healthcare providers, and those living with A.D to reduce mortality. Chen et al. (2021) furthered the conversation by explaining that the brain-heart interaction concept needs exploration and its relationship with Aβ plaques and tau tangle biomarkers.

Research Question

What is the association level between past cardiovascular events, amyloid-β plaques/tau proteins, and an AD diagnosis in participants between 55 and 80 years of age, controlling for age and other confounders?

Nature of the Study and Design

A quantitative approach was used to analyze the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) to explore the effects of past cardiovascular events on the presence of amyloid-β plaques/tau proteins and an AD diagnosis. For this study, the independent variable is cardiovascular health/events (i.e., prior stroke, heart attack, heart disease, high blood pressure, and amyloid-β plaques). The dependent variable was an AD diagnosis. The results intend to aid healthcare providers' understanding of the level of association between prior cardiovascular events and cognitive decline as potential risk factors.

Methods

Population

The target population for this study is a cohort of participants in the NACC's UDS with varying cognitive impairment levels. Study participants have diverse demographic backgrounds, and those considered cognitively normal participate in the study as a control (National Alzheimer's Coordinating Center, 2021). The Alzheimer's Disease Research Centers (ADRCs) collect across the United States from 37 locations.

Sample and Power

Due to the extensive number of participants in the UDS, stratified random sampling was used, controlling for age. Anyone under 55 was excluded from the study as they are below the average age for AD symptoms, similar to the inclusion methods of Lourenco et al. (2018). All participants have either experienced cognitive decline or no cognitive issues. Participants include those diagnosed with AD or dementia and have completed surveys regarding their past cardiovascular health.

The power levels for this analysis were based on $\delta = 0.3$, $\delta = 0.5$, and $\delta = 0.8$, which is consistent with Cohen's small, medium, and large effect sizes. The effect size ensures the rejection of a false null hypothesis or Type 1 error (Anderson et al., 2017). G* Power Statistics 3.1 was used to calculate appropriate sample sizes guided by the G*Power Statistics Manual (2021). The selected statistical test is Logistic Regression, and the type of power analysis was an "A priori." The effect size input mode was "Two Probabilities," which is the probability of an event under H_0 and H_1, in terms of p_1 and p_2, which is a two-tailed test, $\Pr(Y = 1 \mid X = 1)\, H1 = 0.1$ and $\Pr(Y = 1 \mid X = 1)\, H0 = 0.05$. An alpha ($\alpha$) level of 0.05 is used to reject or accept the null hypothesis. The significance level $\alpha = 0.05$ indicates a 5% probability of type I error where the null hypothesis is incorrectly rejected (Anderson, 2017). The last input includes *power (1-β err prob):* 0.95, R^2 other X: 0, X Distribution: Binomial, and *X parm π: 0.5* to generate a sample size needed to achieve reliable results (G*Power 3.1 Manual, 2021). The total sample size for logistic regression is a *Critical z:* 1.95996, *Total samples size:* $N = 1299$, and *Actual power:* 0.950068.

Sources of Data

The study used a quantitative approach. It involved using publicly available National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and census data from the United States Census Bureau 2020. The data was de-identified and contained a systematic random sampling of participants.

Instrumentation

Data was requested through the National Alzheimer's Coordinating Center (NACC). After contacting the NACC and providing a detailed report outlining the purpose and intentions for the data's use, they provided an SPSS Investigator NACC sav. file for analysis (NACC, 2021). The survey questions in the UDS include demographic information (e.g., sex and year of birth), history of heart attack/cardiac arrest, history of stroke, congestive heart failure, hypertension, abnormally elevated amyloid on PET, tau PET evidence for AD, and Presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease (Table 1). Variable type codes include female/male and year for demographics; all others were recoded as 0=Absent, 1= Recent/Active, and 2=Remote/Inactive for independent variables. Due to the series of bivariate tests in the study, patients with codes 9 and -4 unknown were not included in this study, and the dependent variables are coded 0 = No and 1 = Yes. Also unincluded are 8 = Unknown/not assessed and -4 = Not applicable: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question are not included.

Table 1

NACC UDS Researcher's Data Dictionary Derived Variables

Form	Variable Name	Short Descriptor	Variable Type	Allowable Codes	Source
A1 Subject Demographics	BIRTHYR	Subject's year of birth	Original UDS question	1875 to (current year minus 15)	v1-3
A1 Subject Demographics question	SEX	Subject's sex	Original UDS	1=Male 2=Female	v1-3
A5 Subject Health History	CVHATT	Heart attack/cardiac arrest	Original UDS question	0=Absent 1=Recent/Active 2=Remote/Inactive 9=Unknown -4= Not available: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v1-3
A5 Subject Health History	CBSTROKE	Stroke	Original UDS question	0=Absent 1=Recent/Active 2=Remote/Inactive 9=Unknown -4= Not available: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v1-3
A5 Subject Health History	CVCHF	Congestive heart failure	Original UDS question	0=Absent 1=Recent/Active	v1-3

				2=Remote/Inactive 9=Unknown -4= Not available: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	
A5 Subject Health History	HYPERTEN	Hypertension	Original UDS question	0 = No 1 = Yes 8 = Unknown/not assessed -4 = Not applicable: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v1-3
D1 Clinician Diagnosis	AMYLPET	Abnormally elevated amyloid on PET	Original UDS question	0 = No 1 = Yes 8 = Unknown/not assessed -4 = Not applicable: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v3
D1 Clinician Diagnosis	TAUPETAD	Tau PET evidence for AD	Original UDS question	0 = No 1 = Yes 8 = Unknown/not assessed -4 = Not applicable: UDS form submitted did	v3

				not collect data in this way, or a skip pattern precludes response to this question	
D1 Clinician Diagnosis	NACCALZD	Presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease	NACC derived variable	0 = No (assumed assessed and found not present) 1 = Yes 8 = No cognitive impairment	v1-3

Design Analysis

The quantitative analysis identifies links between cardiovascular health, amyloid-β plaques/tau proteins, and AD diagnosis. Bivariate logistic regression, Omnibus Tests of Model Coefficients, and Cox and Snell's /Nagelkerke's were used to test overall statistical significance and the strength of association between variables. IBM Statistical Package for Social Sciences (SPSS) 27 was used to determine an odds ratio output (i.e., β-values) between dependent and independent variables and answer the following research questions:

Research Question: Based on the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), what are the association levels between past cardiovascular events, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants who are between the ages of 55 and 80 years of age controlling for age and other confounders?

$H_0$1 – Based on the NACC Uniform Data Set, there are no associations between cardiovascular health, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

H_a1 – Based on the NACC Uniform Data Set, there are associations between cardiovascular health, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

The data were screened for missing, unknown, and outlying data. The chosen statistical test is a binary logistic regression, and the statistical significance level is $\alpha = 0.05$. A binary logistic regression is applicable when testing the outcome of a dichotomous variable (i.e., presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease). Testing for assumptions was conducted before running the regression. According to Laerd Statistics (2022), assumptions include a dichotomous dependent variable, contentious or nominal independent variables, independence between the observations, a minimum number of participants, linearity between the independent and dependent variables, independence, no multicollinearity, and no significant outliers. The rationale for selecting the covariates age and gender stems from Cladwell et al. (2017), who indicate age and gender influence AD biomarkers.

Results

Execution

Once I received Institutional Review Board approval, study #03-10-22-0978803, I completed the required data request through the National Alzheimer's Coordinating Center (NACC). After contacting the NACC and providing a detailed report outlining the

purpose and intentions for the data's use, they provided an SPSS Investigator NACC sav. file for analysis (NACC, 2021). The total number of participants included in the data set was 164,265.

The G* Power Statistics calculated prior to the data collection applied sample sizes guided by the G*Power Statistics Manual (2021). The selected statistical test was Logistic Regression, and the effect size input mode was "Two Probabilities," which is the probability

of an event under H_0 and H_1, in terms of p_1 and p_2, which is a two-tailed test, $\Pr(Y = 1 \mid X = 1)\, H1 = 0.1$ and $\Pr(Y = 1 \mid X = 1)\, H0 = 0.05$. An alpha (α) level of 0.05 was used to reject or accept the null hypothesis. The significance level α = 0.05 indicates a 5% probability of type I error where the null hypothesis is incorrectly rejected (Anderson, 2017). The last input included *power (1-β err prob):* 0.95, R^2 other X: 0, X Distribution: Binomial, and *X parm π: 0.5* to generate a sample size needed to achieve reliable results (G*Power 3.1 Manual, 2021).

The total sample size for logistic regression is a *Critical z:* 1.95996, *Total samples size:* $N = 1229$, and *Actual power:* 0.950068 for the dependent variables AMYLPET (Abnormally elevated amyloid on PET) and NACCALZD (Presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease). Due to the lack of participants who received testing for the dependent variable TAUPETAD (Tau PET evidence for AD), the variable is not used in the study as there is not enough power to provide results avoiding a type I or type II error. All independent variables are present in the analysis for the 1,229 randomly selected participants.

Results

The total sample size from the NACC Uniform Data Set is 1,229 participants (Table 2). Participants include only those assessed for the presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease, the dependent variable, and the independent variables heart attack/cardiac arrest, stroke, congestive heart failure, hypertension, abnormally elevated amyloid on PET. As previously stated, excluded participants are those assessed for tau PET evidence for AD due to a low rate of tau assessment. The dependent variable was re-coded as 0 = No AD and 1 = Yes AD (Table 3). The model includes the constant without adding the independent variables (Table 4). The classification table assumes that all participants have AD, and the model only correctly classified cases 51.3% of the time (Laerd Statistics, 2022). After selecting the sample size, I tested assumptions per Laerd Statistics (2022). Assumptions met the requirements of a dichotomous dependent variable, contentious or nominal independent variables, independence between the observations, a minimum number of participants, linearity between the independent and dependent variables, independence, no multicollinearity, and no significant outliers.

Table 2

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	1229	100.0
	Missing Cases	0	.0
	Total	1229	100.0
Unselected Cases		0	.0
Total		1229	100.0

a. If weight is in effect, see classification table for the total number of cases.

Table 3

Dependent Variable Encoding

Original Value	Internal Value
No AD	0
Yes AD	1

Table 4

Classification Table[a,b]

			Predicted NACCALZD		
	Observed		No AD	Yes AD	Percentage Correct
Step 0	NACCALZD	No AD	0	602	.0
		Yes AD	0	627	100.0
	Overall Percentage				51.0

a. Constant is included in the model.

b. The cut value is .500

Data Analysis

Three tests were used to identify the model fit for the use of bivariate logistic regression and independent and dependent variables. The Omnibus Tests of Model Coefficients indicate the overall significance of the model (Laerd Statistics, 2022). The results show that the model is significant (i.e., $p < .0005$), meaning the model is a good fit for the use of bivariate logistic regression (Table 5). The Hosmer and Lemeshow goodness of fit test also indicates that the model is not a poor fit as it is not significantly poor with a $p > 0.05$ or $p = .646$ (Table 6). Lastly, to understand the level of variation explained by the dependent variable on the model, I ran a Model Summary with Cox & Snell R Square and Nagelkerke R Square values (Laerd Statistics, 2022). The results indicate that the explained variation in the dependent variable ranges from 47.9% for Cox & Snell R Square values and 63.9% for Nagelkerke R Square values (Table 7).

Since bivariate logistic regression is a way to estimate the probability of an event occurring, I created a classification table to assess the model's effectiveness. It is common to use logistic regression to predict outcomes based on independent variables (Laerd Statistics, 2022). The cut value is .500, indicating that the probability of classifying a yes AD value is greater than .500. Previously, the classification table without the independent variables (Table 4) showed that only 51.3% of cases would correctly be classified by assuming that all cases we yes AD. Including the independent variables in the model enhances the ability to classify a patient’s probability of having or not having AD from 51.3% without independent variables to 87.8% with independent variables (Table 8).

Table 5

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	801.118	6	.000
	Block	801.118	6	.000
	Model	801.118	6	.000

Table 6

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	5.114	7	.646

Table 7

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	901.751a	.479	.639

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Table 8

Classification Table[a]

			Predicted		
			NACCALZD		Percentage
	Observed		No AD	Yes AD	Correct
Step 1	NACCALZD	No AD	534	64	89.3
		Yes AD	86	545	86.4
	Overall Percentage				87.8

a. The cut value is .500

Findings

Bivariate logistic regression in SPSS produced a “Variables in the Equation” table that indicates the level of contribution each independent variable has in the model and their statistical significance (Laerd Statistics, 2022). The Wald test provides the significance of each variable to the model. It shows that none of the variables, aside from detecting amyloid-beta plaques in a patient’s brain, are statistically significant (Table 9). The odds ratio or "Exp(B)" column, along with confidence intervals (i.e., 95% C.I.), indicates the change in the odds for each increase in one unit of the independent variable (Laerd Statistics, 2022). The results show that the independent variable with the significant odds ratio is the presence of amyloid-beta plaques, followed by independently non-significant hypertension (HYPERTEN) at 1.412, having had a stroke (CBSTROKE) at 1.304, and heart attack (CVHATT) at 1.285. Congestive heart failure (CVCHF) had an odds ratio of 1.009, and gender (SEX) had an odds ratio of .850 based on the female gender coded as female = 2. Overall, the logistic regression model was statistically significant, $X^2(6) = 801.118\, p < .0005$

Table 9

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	SEX	-.162	.177	.844	1	.358	.850	.601	1.202
	CVHATT	.251	.364	.476	1	.490	1.285	.630	2.621
	CBSTROKE	.266	.333	.636	1	.425	1.304	.679	2.507
	CVCHF	.009	.541	.000	1	.987	1.009	.349	2.914
	HYPERTEN	.345	.181	3.614	1	.057	1.412	.989	2.015
	AMYLPET	4.014	.180	495.631	1	.000	55.380	38.893	78.855
	Constant	-1.772	.314	31.837	1	.000	.170		

a. Variable(s) entered on step 1: SEX, CVHATT, CBSTROKE, CVCHF, HYPERTEN, AMYLPET.

Discussion

Potential risk factors associated with Alzheimer's disease were quantifiably analyzed to identify levels of association between participant’s cardiovascular events and an AD diagnosis. The postulation and framework that there is a positive correlation between cardiovascular health and AD indicate a need to evaluate cardiovascular risk factors as a potential protective factor to improve the detection and prevention of AD (Finch & Kulminski, 2019). Recognizing risk and the levels of association as a means of early AD detection can provide insight to healthcare providers aiming to diagnose and treat patients earlier before the disease progresses. The creation of early intervention may enhance patient and family members’ quality of life in many respects when healthcare providers and patients are aware of associated risks and how to enhance people’s quality of life both physically and economically.

Interpretation

Although the overall model was statistically significant, the individual components were not, excluding the presence of amyloid-beta plaques in the brain. Regardless of significance, the model does highlight the level of a positive and negative association between cardiovascular events and gender. Combining the independent variables improves predicting the potential diagnosis of AD seen in the Omnibus Tests of Model Coefficients significance. The odds ratio indicates that patients with hypertension (HYPERTEN) at 1.412, having had a stroke (CBSTROKE) at 1.304, and heart attack (CVHATT) at 1.285 could be at an increased risk of AD. Additionally, the effect and sample size provide the power to make a case that the independent variables influence the dependent variable (Anderson et al., 2017). Caldwell et al. (2017) explain that AD differs between men and women, as does cognitive decline associated with abnormal amyloid-beta plaque levels. The authors indicate that gender is an essential factor for early detection and that monitoring risk factors aid in creating treatments to slow the progression of AD. The findings in this study show a slight negative correlation between an AD diagnosis and gender, indicating that female participants were less likely to have been diagnosed with cognitive decline.

The literature review indicates positive correlations between cardiovascular risk factors such as having had a heart attack, stroke, or hypertension potentially associated with elevated amyloid-beta plaque levels. Chen et al. (2017), Finch and Kulminski (2019), and Lourenco et al. (2018) indicated that heart health is an essential factor that can indicate the potential for cognitive decline and AD. Finch and Kulminski (2019)

specifically highlighted the importance of monitoring cardiovascular health and contend that the heart-brain interaction is closely related, and problems with one affect the other. The research in this manuscript could provide evidence that there is a need to monitor patients more closely for early cognitive decline and AD when affected by cardiovascular issues or events.

Limitations

The primary limitation is this study that the lack of participants assessed for tau proteins via a PET scan. Limiting co-variates and age limits may increase the sample size and provide the same power in future studies. Tini et al. (2020) indicated an association between the formation of tau proteins, cardiovascular health, and the presence of amyloid-beta plaque. They indicate a lack of research regarding the association between tau proteins and cognitive decline or AD, a limitation based on limited testing for tau in the brain. Additional limitations include spatial analysis that would provide a more comprehensive look at patients' location and potential increases in exposure to environmental risk factors associated with AD. The National Alzheimer's Coordinating Center UDS does not include patients' location and is a limitation for understanding where clusters occur and additional risk factors.

Implications

This study potentially promotes social change by contributing to the knowledge surrounding risk and protective factors associated with AD. As people live longer and more people are diagnosed with AD, there is a need to identify early potential risk factors for creating interventions and therapies to decrease the progression of cognitive decline

and burden on individuals and society (National Institute on Ageing [NIH], 2017). Apparent correlations between risk factors such as cardiovascular health and events provide information and indicators to health care providers regarding the potential of AD development (Finch & Kulminski, 2019). This study supports using current and pre-existing cardiovascular health issues as bio-markers for assessing patients for cognitive decline over the age of 55. Although there are not many significant correlations in this study's model, the results show positive levels of correlation between cardiovascular variables. Implementing screening for cognitive health and AD when cardiovascular risk factors are present could be a novel way of influencing the monitoring and pre-diagnosis of AD.

This study provides implications for early AD detection. It contributes to an understanding that there is a need for action on the part of health care providers and patients regarding the promotion of detection and intervention of AD. There is a gap in knowledge concerning the exact determinants of health associated with the onset and presence of AD (Tini et al., 2020). The participants in this study are unique as the random selection, and associated variables have not previously been tested together, providing a novel assessment of the level of correlation between cardiovascular health and events associated with AD diagnosis. Finch and Kulminski (2019) indicate a need to understand what risk factors influence AD and that there is an amalgamation of physical and environmental exposures that contribute to the disease. There is a need to continue to explore potential risk factors to more precisely identify the underlying mechanisms of

AD to decrease the burden of the disease at the individual and societal level and promote positive social change.

Recommendations

There is a need for future studies to examine the effects of cardiovascular health and AD outcomes. This study does not include numerous factors, such as race and ethnicity, educational level, and physical activity. Lourenco et al. (2018) explained that sociodemographic variables correlate highly with cardiovascular health and cognitive capabilities. Including sociodemographic variables in the model could increase the ability of healthcare providers to identify the risk for AD and provide therapeutic interventions before the disease progresses. Additional recommendations include using other statistical analyses such as linear regression, which uses continuous variables to predict a possible AD outcome. According to Laerd Statistics (2022), a simple linear regression applies two variables to determine an outcome for a dependent variable. Instead of having a complete bivariate model, the linear regression could independently assess the relationship between continuous variables and levels of cognitive decline rather than have yes or no outcomes. The limitation is the lack of information associated with the levels of cognitive decline, which is an additional consideration/recommendation for collecting data that measures participants' cognitive impairment levels.

Conclusion

Alzheimer’s disease is a growing epidemic and is the sixth-leading cause of death in the United States. Individuals with AD often have comorbidities due to aging, with cardiovascular health hypothesized to correlate with the disease's development.

Participants provided health information collected in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). The data included questions about the participant's cognitive health status, an AD diagnosis, and current and past physical health questions (e.g., a heart condition or event). A random selection of (n = 1,229) participants included (n = 602) not diagnosed with AD and (n = 627) who were diagnosed with AD. A bivariate linear regression was conducted to identify the level of association between cardiovascular health variables and an AD diagnosis. The overall model found significance between the combined cardiovascular health variables, including the presence of amyloid-beta plaques and an AD diagnosis. The were no significant correlations between individual cardiovascular health variables other than the presence of amyloid-beta plaques. However, levels of association measured with an odds ratio indicate positive correlations between poor cardiovascular health and past cardiovascular events. Future research is needed to identify the association between additional cardiovascular variables to improve understanding of the heart-brain connection and the presence of amyloid-beta plaques and AD diagnosis. Understanding the heart-brain connection could improve health care providers' ability to detect AD earlier and improve therapies and patients' quality of life.

References

Anderson, S. F., Kelley, K., & Maxwell, S. E. (2017). Sample-size planning for more accurate statistical power: A method adjusting sample effect sizes for publication bias and uncertainty. *Psychological Science, 28*(11), 1547–1562. https://doi.org/10.1177/0956797617723724

Bronfenbrenner, U. (1977). Toward an experimental ecology of human development. *American Psychologist, 32*(7), 513-531.

Caldwell, J. Z. K., Berg, J.-L., Cummings, J. L., & Banks, S. J. (2017). Moderating effects of sex on the impact of diagnosis and amyloid positivity on verbal memory and hippocampal volume. *Alzheimer's Research & Therapy, 9*, 1–10. doi:10.1186/s13195-017-0300-8

Chen, M., Hu, C., Dong, H., Yan, H., Wu, P., & Alzheimer's Disease Neuroimaging Initiative (2021). A history of cigarette smoking is associated with faster functional decline and reduction of entorhinal cortex volume in mild cognitive impairment. Aging, 13(4), 6205–6213. https://doi.org/10.18632/aging.202646

Chen, Z., Venkat, P., Seyfried, D., Chopp, M., Yan, T., & Chen, J. (2017). Brain–Heart Interaction. *Circulation Research, 121*(4), 451-468. https://doi.org/10.1161/circresaha.117.311170

Ferrucci, L., & Fabbri, E. (2018). Inflammageing: Chronic Inflammation in Ageing, Cardiovascular Disease, and Frailty. Nature Reviews Cardiology, *15*, 505–522. https://doi.org/10.1038/s41569-018-0064-2

Finch, C. E., & Kulminski, A. M. (2019). The Alzheimer's Disease Exposome. *Alzheimer's & dementia: the journal of the Alzheimer's Association*, *15*(9), 1123–1132. https://doi.org/10.1016/j.jalz.2019.06.3914

G*Power 3.1 Manual. (2021). General psychology and industrial psychology. Technical Manual. https://www.psychologie.hhu.de/fileadmin/redaktion/Fakultaeten/Mathematisch-Naturwissenschaftliche_Fakultaet/Psychologie/AAP/gpower/GPowerManual.pdf

Jørgensen, I.F., Aguayo-Orozco, A., Lademann, M., Brunak, S. (2020). Age-stratified longitudinal study of Alzheimer's and vascular dementia patients. Alzheimer's Dement, *16*: 908– 917. https://doi.org/10.1002/alz.12091

Laerd Statistics. (2022). Binomial Logistic Regression. Retrieved from https://statistics.laerd.com/premium/index.php

Lourenco, J., Serrano, A., Santos-Silva, A., Gomes, M., Afonso, C., Freitas, P., Paul, C., & Costa, E. (2018). Cardiovascular Risk Factors Are Correlated with Low Cognitive Function among Older Adults Across Europe Based on The SHARE Database. *Aging and Disease*, *9*(1), 90–101. https://doi.org/10.14336/AD.2017.0128

National Alzheimer's Coordinating Center (2021). Description of the NACC database. Retrieved from https://www.alz.washington.edu/WEB/data_descript.html

National Institute on Ageing (2017). What is Alzheimer's Disease? https://www.nia.nih.gov/health/what-alzheimers-disease

Stakos, D., Stamatelopoulos, K., Bampatsias, D., Sachse, M., Zormpas, E.,

Vlachogiannis, N., Tual-Chalot, S., & Stellos, K. (2020). The Alzheimer's disease Amyloid-Beta hypothesis in cardiovascular aging and disease. *Journal of the American College of Cardiology, 75*(8), 952-967. https://doi.org/10.1016/j.jacc.2019.12.033

Tini, G., Scagliola, R., Monacelli, F., La Malfa, G., Porto, I., Brunelli, C., & Rosa, G. M. (2020). Alzheimer's Disease and Cardiovascular Disease: A Particular Association. Cardiology Research & Practice, 1–10. https://doi.org/10.1155/2020/2617970

Troncone, L., Luciani, M., Coggins, M., Wilker, E. H., Ho, C.-Y., Codispoti, K. E., Frosch, M. P., Kayed, R., & Del Monte, F. (2016). Aβ Amyloid Pathology Affects the Hearts of Patients With Alzheimer's Disease. *Journal of the American College of Cardiology*, *68*(22), 2395-2407. https://doi.org/10.1016/j.jacc.2016.08.073

Modifiable Substance Risk Factors and Alzheimer's Disease

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Outlet for Manuscript

Primary Healthcare Providers and Cognitive Researchers: This scholarly, peer-reviewed journal with a targeted audience of primary healthcare providers and cognitive researchers in academia or other settings focuses on topics related to modifiable substance abuse risk factors and evaluation (i.e., alcohol consumption, tobacco use, and the use of an anxiolytic, sedative, or hypnotic agent). Accepted types of manuscripts are original research, quantitative database analysis, and statistical analysis. Submission guidelines for the *Journal of Substance Use* (JSU), a peer-reviewed, open-access journal. Manuscripts must include:

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Abstract

Alzheimer's disease (AD) is a growing epidemic and is the sixth-leading cause of death in the United States. Individuals with AD often have comorbidities due to the aging process. There is a lack of research related to understanding comorbidities as associated risk factors for AD. This study is guided by Finch and Kulminski's (2019) AD Exposome as a caveat to explore a patient's behavioral history of smoking cigarettes, alcohol abuse, and use of an anxiolytic, sedative, or hypnotic agent and an AD diagnosis. Participants provided health information collected in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). The data included questions about the participant's current cognitive health status, including an AD diagnosis, and current and past behavioral health questions (e.g., smoking history). A random selection of (n = 1,229) participants included (n = 611) not diagnosed with AD and (n=618) who were diagnosed with AD. Participants also include (n = 625) not diagnosed with elevated amyloid and (n = 604) who were. A bivariate linear regression was conducted to identify the level of association between modifiable behavior variables and an AD diagnosis and elevated amyloid PET. The overall AD model found the combined modifiable health variables and an AD diagnosis significance. Levels of association measured with an odds ratio indicate positive correlations between the current reported use of an anxiolytic, sedative, or hypnotic agent and a negative correlation between smoking and alcohol abuse. Future research is needed to identify the association between additional modifiable health variables to improve the understanding of the behavioral health risks and the presence of amyloid-beta plaques and AD diagnosis.

Introduction

Alzheimer's disease is a growing epidemic and is the sixth-leading cause of death in the U.S., with diagnoses expected to triple by 2060 to over 14 million people. Individuals with AD often have modifiable risk factors in concert with the aging process. A risk factor associated with AD is long-term substance abuse. Cigarette smoking, alcohol abuse, and anxiolytic, sedative, or hypnotic agents (e.g., diphenhydramine) are three of the most prevalent and easily accessible substances associated with AD neurological side effects (Kawase et al., 2021; Larsson et al., 2017). Smoking and alcohol use are well-known to be considered harmful, but the extent is unclear. The effects of diphenhydramine on AD are newly researched and chosen for this study due to its prevalence in commonly used nonprescription drugs (e.g., Benadryl, Tylenol, Unisom, and Advil, to name a few). Larsson et al. (2017) found that the odds of AD diagnosis correlate with modifiable behaviors, most significantly cigarette smoking and alcohol use. Kawase et al. (2021) found that diphenhydramine directly affects the blood-brain barrier (BBB) while influencing brain inflammation and potentially altering the risk of AD and dementia. Zheng et al. (2021) examined anticholinergic drugs and the confounding variables of alcohol consumption and tobacco use. The authors found an increase in AD in participants exposed to anticholinergic drugs. They suggest that substance abuse and standard nonprescription medicines, such as anticholinergics, are a potential AD risk due to accessibility and should be used cautiously. The limited research on the interaction level between commonly used substances and anticholinergic drugs related to AD requires quantitative exploitation.

Significance

This study provides original statistical data and quantitative analysis that promotes a physiological and psychological approach to AD research by assessing the relationship between modifiable risk factors health and an AD diagnosis. Insights from this study intend to help researchers and health practitioners identify modifiable risk factors associated with AD and encourage healthy lifestyles to decrease AD prevalence. The primary goal is to increase AD prevention and early detection to improve people's quality of life, social determinants of health, and health outcomes. Modifiable risk factors such as stress, smoking, alcohol abuse, and other lifestyle choices influence the presence of amyloid-beta (Aβ) plaques in the brain and AD (Amakiri et al., 2019). However, a limited number of studies address the specific level of relationship between modifiable risk factors, life events, and the presence of AD and Aβ deposits.

This study's theoretical framework applies Finch and Kulminski's (2019) AD exposome. Finch and Kulminski's (2019) AD exposome is used as a guide to explore a patient's modifiable risk factors and an AD diagnosis. The authors indicated that risk factors that require research are Exogenous AD-Exposome factors at the micro-levels, including pollutants, a person's diet, and other environmental risks. The hypothesis for this study uses the AD Exposome to guide the thought process of associating smoking, heavy alcohol use, and diphenhydramine as potential risk factors for cognitive decline and development of AD. Bronfenbrenner's (1977) ecological systems theory theoretical framework works with Finch and Kulminski's (2019) AD exposome by proposing that a person's environment affects lifestyle choices and social determinants of health and

health outcomes. The two theories work synergistically as a structure for this study by providing evidence that there are correlations between modifiable risk factors and associations with Aβ plaques and tau tangle biomarkers associated with the early onset and diagnosis of AD.

There is no clear understanding of the level of modifiable risk concerning the early onset of AD and cognitive decline. Finch and Kulminski (2019) explain that environmental and modifiable risk factors contribute to AD aging and AD-genetic risk and suggest that brain aging and cognitive decline are vulnerable to multiple variables. The authors specifically look at traumatic brain injury (TBI), cigarette smoke, and air pollution. They indicate that these risk factors are associated with ApoE4, a gene that influences the production of a protein called apolipoprotein E (Finch and Kulminski, 2019). Tachibana et al. (2019) explain that the apolipoprotein E gene increases the risk of late-onset AD and increases the amount of amyloid-β (Aβ) peptides in the brain. Finch and Kulminski (2019) indicate a need for more research focusing on extraneous factors beyond genetics to understand AD risk better. Modifiable exogenous risk factors may affect cognitive decline and AD diagnosis by promoting the presence of Aβ plaques biomarkers associated with AD (Finch & Kulminski, 2019). The extent of such modifiable risk factors is in question, provoking a need to research levels associated with AD diagnosis to determine the benefits of modifiable risk interventions.

Relevant Scholarship

Similar to Finch and Kulminski's (2019) finding, Larsson et al. (2017) found an association between modifiable risk factors, specifically cigarette smoking, alcohol use,

and AD diagnosis. Finch and Kulminski's (2019) used a Mendelian randomization analysis to identify the level of association between modifiable risk factors with a Bonferroni corrected significance level of $p < 0.05$. They found a direct positive correlation between the number of cigarettes smoked, the amount of alcohol regularly consumed, and the risk of AD. Although Larsson et al. (2017) found significant correlations, particular levels of the association are unclear. They suggest that additional research is needed to determine the levels of association behavioral risk factors have on the presence of Aβ plaques and cognitive decline to build on research gaps and improve health outcomes.

Neurological degradation and impaired cognitive function are associated with AD and the presence of Aβ plaques and tau tangles (Peng et al., 2020). The authors hypothesize that numerous environmental and modifiable behaviors are risk factors. Langballe et al. (2015) explain that chronic alcohol use and smoking increase the risk of impaired cognitive function and AD by disrupting nerve signals in the brain. In an epidemiological literature review, Peng et al. (2020) found that exposure to alcohol and cigarette smoke in human and mice trials increased the presence of Aβ plaques and tau tangles and the odds of AD and progression of cognitive decline. Independently, cigarette smoke contributed to adverse brain atrophy and AD onset via the thinning of cortices (Durazzo et al., 2018). The literature indicates that modifiable behaviors influence the risk of developing AD and abnormal cognitive decline and that more research is needed to determine the associated risk levels.

Anticholinergic drugs that contain diphenhydramine are commonly used and available without a prescription. The long-term use of DPHM is a potential risk factor for the development of dementia and cognitive decline (Wong, 2015). Antihistamines, sleep aids, and antidepressants are some of the most common medications containing diphenhydramine (i.e., an anxiolytic-hypnotic drug). Wong (2015) contends the need to use anticholinergic drugs cautiously due to the potential for cognitive interference. Zheng et al. (2021) examined anticholinergic drug use and indicated a connection between heavier use and all types of dementia, including AD and the early onset of cognitive decline. The authors suggest that anticholinergic drug use is a modifiable risk factor for AD. An early prevention strategy is limiting exposure. Bauer (2018) explained explicitly that anxiolytic-hypnotic exposure affects changes in behavior and memory dysfunction and proposes a need for further research.

There is limited research on the interaction between the risk modifiable factors of alcohol, cigarette, and anxiolytic-hypnotic use related to AD (Bauer, 2018; Langballe et al., 2015). The authors contend that research is needed to promote public health by identifying individual behaviors as a potentially modifiable risk factor for AD. The intended outcome is to limit exposure in the general community and promote interventions by informing healthcare providers and those living with A.D to reduce mortality.

Research Question

What is the association level between alcohol, cigarette, and anxiolytic-hypnotics use concerning amyloid-β plaques/tau proteins and an AD diagnosis in participants between 55 and 80 years of age, controlling for age and other confounders?

Nature of the Study and Design

I used a quantitative approach to analyze the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) to explore past, and present alcohol, cigarette, and anxiolytic-hypnotics use on the presence of amyloid-β plaques/tau proteins and an AD diagnosis. For this study, the independent variables are modifiable risk factors (i.e., alcohol, cigarette, and anxiolytic-hypnotics use). The dependent variable is the presence of amyloid-β plaques/tau proteins and an AD diagnosis. The results intend to aid healthcare providers' understanding of the level of association between modifiable risk factors and cognitive decline.

Methods

Population

The target population for this study is a cohort of participants in the NACC's UDS who have varying cognitive impairment levels. Study participants have diverse demographic backgrounds, and those considered cognitively normal participate in the study as a control (National Alzheimer's Coordinating Center, 2021). The Alzheimer's Disease Research Centers (ADRCs) collect across the United States from 37 locations.

Sample and Power

Stratified random sampling was used in this study while controlling for age. Participants under 55 were excluded due to the lack of AD prevalence in younger populations (Lourenco et al., 2018). The study does not discriminate between those with or without cognitive decline. Only participants who have completed surveys for the modifiable behavior (i.e., alcohol, cigarette, and anxiolytic-hypnotics use) were included.

The power levels for this analysis were based on $\delta = 0.3$, $\delta = 0.5$, and $\delta = 0.8$, which is consistent with Cohen's small, medium, and large effect sizes. The effect size ensures the rejection of a false null hypothesis or Type 1 error (Anderson et al., 2017). G* Power Statistics 3.1 was used to calculate appropriate sample sizes guided by the G*Power Statistics Manual (2021). The selected statistical test is Logistic Regression, and the type of power analysis was "A priori." The effect size input mode was "Two Probabilities," which is the probability of an event under H_0 and H_1, in terms of p_1 and p_2, which is a two-tailed test, $\Pr(Y = 1 \mid X = 1)\, H1 = 0.1$ and $\Pr(Y = 1 \mid X = 1)\, H0 = 0.05$. An alpha (α) level of 0.05 was used to reject or accept the null hypothesis. The significance level $\alpha = 0.05$ indicates a 5% probability of type I error where the null hypothesis is incorrectly rejected (Anderson, 2017). The last input includes *Power (1-β err prob):* 0.95, R^2 other X: 0, X Distribution: Binomial, and *X parm π: 0.5* to generate a sample size needed to achieve reliable results (G*Power 3.1 Manual, 2021). The total sample size for logistic regression is a *Critical z:* 1.95996, *Total samples size:* $N = 1299$, and *Actual power:* 0.950068.

Sources of Data

The study used a quantitative approach. It involved using publicly available National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and census data from the United States Census Bureau 2020. The data is de-identified and contains a systematic random sampling of participants.

Instrumentation

Data was requested through the National Alzheimer's Coordinating Center (NACC), and it required a detailed report outlining the purpose and intentions for the data's use. The NACC provided an SPSS Investigator NACC sav. file for analysis (NACC, 2021). The data in the UDS includes information concerning demographics (e.g., sex and year of birth), alcohol, cigarette, and anxiolytic-hypnotics use, abnormally elevated amyloid on PET, tau PET evidence for AD, and presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease (Table 1). Variable type codes include female/male and year for demographics; all others were recorded as 0 = Absent and 1= Recent/Active due to the series of bivariate tests in the study. Patients with codes 9 and -4 unknown were not included in this study.

Table 1

NACC UDS Researcher's Data Dictionary Derived Variables

Form	Variable Name	Short Descriptor	Variable Type	Allowable Codes	Source
A1 Subject Demographics	BIRTHYR	Subject's year of birth	Original UDS question	1875 to (current year minus 15)	v1-3
A1 Subject Demographics question	SEX	Subject's sex	Original UDS	1=Male 2=Female	v1-3
A5 Subject Health History	SMOKYRS	Total years smoked cigarettes	Original UDS question	0–87 88=Not applicable 99=Unknown -4= Not available: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v1-3
A5 Subject Health History	ALCOHOL	Alcohol abuse — clinically significant occurring over a 12-month period manifested in one of the following areas: work, driving, legal, or social	Original UDS question	0=Absent 1=Recent/Active 2=Remote/Inactive 9=Unknown -4= Not available: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v1-3

A4 Subject Medications	NACCAANX	Reported current use of an anxiolytic, sedative, or hypnotic agent	NACC derived variable	0=Did not report use at visit 1=Reported use at visit -4=Did not complete medications form	v1-3
D1 Clinician Diagnosis	AMYLPET	Abnormally elevated amyloid on PET	Original UDS question	0 = No 1 = Yes 8 = Unknown/not assessed -4 = Not applicable: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v3
D1 Clinician Diagnosis	TAUPETAD	Tau PET evidence for AD	Original UDS question	0 = No 1 = Yes 8 = Unknown/not assessed -4 = Not applicable: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v3
D1 Clinician Diagnosis	NACCALZD	Presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease	NACC derived variable	0 = No (assumed assessed and found not present) 1 = Yes 8 = No cognitive impairment	v1-3

Design Analysis

The quantitative analysis identifies links between modifiable behavior, amyloid-β plaques/tau proteins, and AD diagnosis. Bivariate logistic regression, Omnibus Tests of Model Coefficients, and Cox and Snell's /Nagelkerke's were used to test overall statistical significance and the strength of association between variables. IBM Statistical Package for Social Sciences (SPSS) 27 was used to determine an odds ratio output (i.e., β-values) between dependent and independent variables and answer the following research questions:

Research Question: Based on the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), what are the association levels between alcohol, cigarette, and anxiolytic-hypnotics use, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants who are between the ages of 55 and 80 years of age controlling for age and other confounders?

$H_0$1: Based on the NACC Uniform Data Set, there are no associations between alcohol, cigarette, and anxiolytic-hypnotics use, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

H_a1: Based on the NACC Uniform Data Set, there are associations between alcohol, cigarette, and anxiolytic-hypnotics use, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

The data was cleaned for missing, unknown, and outlying variables. The chosen statistical test is a binary logistic regression, and the statistical significance level is $\alpha = 0.05$. A binary logistic regression is applicable when testing the outcome of a

dichotomous variable (i.e., presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease). Testing for assumptions was conducted before running the regression. According to Laerd Statistics (2022), assumptions include a dichotomous dependent variable, contentious or nominal independent variables, independence between the observations, a minimum number of participants, linearity between the independent and dependent variables, independence, no multicollinearity, and no significant outliers. The rationale for selecting the covariates age and gender stems from Cladwell et al. (2017), who indicate age and gender influence AD biomarkers.

Results

Execution

Once I received Institutional Review Board approval, study #03-10-22-0978803, I completed the required data request through the National Alzheimer's Coordinating Center (NACC). After contacting the NACC and providing a detailed report outlining the purpose and intentions for the data's use, they provided an SPSS Investigator NACC sav. file for analysis (NACC, 2021). The total number of participants included in the data set was 164,265.

The G* Power Statistics calculated prior to the data collection applied sample sizes guided by the G*Power Statistics Manual (2021). The selected statistical test was Logistic Regression, and the effect size input mode was "Two Probabilities," which is the probability of an event under H_0 and H_1, in terms of p_1 and p_2, which is a two-tailed test, $\Pr(Y = 1 \mid X = 1)\, H1 = 0.1$ and $\Pr(Y = 1 \mid X = 1)\, H0 = 0.05$. An alpha (α) level of 0.05 was used to reject or accept the null hypothesis. The significance level $\alpha = 0.05$

indicates a 5% probability of type I error where the null hypothesis is incorrectly rejected (Anderson, 2017). The last input included *Power (1-β err prob):* 0.95, R^2 other X: 0, X Distribution: Binomial, and *X parm π: 0.5* to generate a sample size needed to achieve reliable results (G*Power 3.1 Manual, 2021).

The total sample size for logistic regression is a *Critical z:* 1.95996, *Total samples size:* $N = 1229$, and *Actual power:* 0.950068 for the dependent variables AMYLPET (Abnormally elevated amyloid on PET) and NACCALZD (Presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease). Due to the lack of participants who received testing for the dependent variable TAUPETAD (Tau PET evidence for AD), the variable is not used in the study as there is not enough power to provide results avoiding a type I or type II error. All independent variables are present in the analysis for the 1,229 randomly selected participants.

Results

The total sample size from the NACC Uniform Data Set is 1,229 participants (Table 2). Participants include only those assessed for the presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease and abnormally elevated amyloid on PET are the dependent variables. The independent variables are the total years a participant smoked cigarettes, alcohol abuse, and current use of an anxiolytic, sedative, or hypnotic agent. As previously stated, excluded participants are those assessed for tau PET evidence for AD due to a low rate of tau assessment. The dependent variable was re-coded as 0 = No AD and 1 = Yes AD (Table 3) and 0 = No AB and 1 = Yes AB (Table 4). The model includes the constant without adding the independent variables for AD

(Table 5) and abnormally elevated amyloid on PET (Table 6). The classification table assumes that all participants have AD or elevated amyloid, and the model only correctly classified cases 50.3% of the time for AD and 50.9% for elevated amyloid (Laerd Statistics, 2022). After selecting the sample size, I tested assumptions per Laerd Statistics (2022). Assumptions met the requirements of a dichotomous dependent variable, contentious or nominal independent variables, independence between the observations, a minimum number of participants, linearity between the independent and dependent variables, independence, no multicollinearity, and no significant outliers.

Table 2

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	1229	100.0
	Missing Cases	0	.0
	Total	1229	100.0
Unselected Cases		0	.0
Total		1229	100.0

a. If weight is in effect, see classification table for the total number of cases.

Table 3

Dependent Variable Encoding

Original Value	Internal Value
No AD	0
Yes AD	1

Table 4

Dependent Variable Encoding

Original Value	Internal Value
No AB	0
Yes AB	1

Table 5

Classification Table[a,b]

			Predicted NACCALZD		Percentage
	Observed		No AD	Yes AD	Correct
Step 0	NACCALZD	No AD	0	611	.0
		Yes AD	0	618	100.0
	Overall Percentage				50.3

a. Constant is included in the model.

b. The cut value is .500

Table 6

Classification Table[a,b]

			Predicted AMYLPET		Percentage
	Observed		No AB	Yes AB	Correct
Step 0	AMYLPET	No AB	625	0	100.0
		Yes AB	604	0	.0
	Overall Percentage				50.9

a. Constant is included in the model.

b. The cut value is .500

Data Analysis

Three tests were used to identify the model fit for the use of bivariate logistic regression for both dependent variables AD diagnosis and elevated amyloid. The Omnibus Tests of Model Coefficients indicate the overall significance of the model (Laerd Statistics, 2021). The results show that the model is significant (i.e., $p < .05$), meaning the model is a good fit for the use of bivariate logistic regression for AD diagnosis (Table 7). However, the model that included only elevated amyloid as the dependent variable is not significant (i.e., $p > .05$), indicating the model is not a good fit for the use of bivariate logistic regression (Table 8). The Hosmer and Lemeshow goodness of fit test indicate that both models are not a poor fit as they are not significantly poor with a $p > 0.05$ or $p = .788$ and $p = .980$ (Tables 9 and 10). Lastly, I ran a Model Summary with Cox & Snell R Square and Nagelkerke R Square values (Laerd Statistics, 2021). The results indicate that the explained variation in the dependent variable ranges from 0.08% for Cox & Snell R Square values and 1.1% for Nagelkerke R Square values for an AD diagnosis (Table 11). Elevated amyloid results range from 0.06% for Cox & Snell R Square values and 0.07% for Nagelkerke R Square values (Table 12).

Since bivariate logistic regression is a way to estimate the probability of an event occurring, I created a classification table to assess the model's effectiveness. It is common to use logistic regression to predict outcomes based on the independent variables (Laerd Statistics, 2022). The cut value is .500, indicating that the probability of classifying a yes AD value is greater than .500. Previously, the classification table without the independent

variables (Tables 5 and 6) showed that only 50.3% and 50.9% of cases would correctly be classified by assuming all cases were AD and AB. Including the independent variables in the model enhances the ability to classify a patient's probability of having or not having AD or AB slightly to 52.2% for AD and 51.7% of cases for AB (Tables 13 and 14).

Table 7

Omnibus Tests of Model Coefficients for AD

		Chi-square	df	Sig.
Step 1	Step	10.028	4	.040
	Block	10.028	4	.040
	Model	10.028	4	.040

Table 8

Omnibus Tests of Model Coefficients for AB

		Chi-square	df	Sig.
Step 1	Step	6.790	4	.147
	Block	6.790	4	.147
	Model	6.790	4	.147

Table 9

Hosmer and Lemeshow Test for AD

Step	Chi-square	df	Sig.
1	3.166	6	.788

Table 10

Hosmer and Lemeshow Test for AB

Step	Chi-square	df	Sig.
1	1.130	6	.980

Table 11

Model Summary for AD

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	1693.688[a]	.008	.011

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Table 12

Model Summary for AB

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	1696.607[a]	.006	.007

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Table 13

Classification Table[a] for AD

			Predicted		
			NACCALZD		Percentage
	Observed		No AD	Yes AD	Correct
Step 1	NACCALZD	No AD	346	265	56.6
		Yes AD	322	296	47.9
	Overall Percentage				52.2

a. The cut value is .500

Table 14

Classification Table[a] for AB

			Predicted		
			AMYLPET		Percentage
	Observed		No AB	Yes AB	Correct
Step 1	AMYLPET	No AB	375	250	60.0
		Yes AB	344	260	43.0
	Overall Percentage				51.7

a. The cut value is .500

Findings

Bivariate logistic regression in SPSS produced a “Variables in the Equation” table that indicates each independent variable's contribution to the model and their statistical significance (Laerd Statistics, 2022). The Wald test provides the significance of each variable to the model. None of the variables are significant regarding correlations between modifiable risk factors and an AD diagnosis (Table 15). The same was found for elevated amyloid, except for the independent variable alcohol abuse. The odds ratio or "Exp(B)" column, along with confidence intervals (i.e., 95% C.I.), indicates the change in

the odds for each increase in one unit of the independent variable (Laerd Statistics, 2022). The results for AD diagnosis show that the independent variable with the non-significant odds ratio is the presence of alcohol abuse (ALCOHOL) with Exp(B) = .739, followed by the current reported use of an anxiolytic, sedative, or hypnotic agent (NACCAANX) at 1.196, and total years smoked cigarettes (SMOKYRS) at 0993. The results for elevated amyloid show that the independent variable with the significant odds ratio is the presence of alcohol abuse (ALCOHOL) with Exp(B) = .703, followed by the non-significant odds ratio of current reported use of an anxiolytic, sedative, or hypnotic agent (NACCAANX) at 1.094, and total years smoked cigarettes (SMOKYRS) at 0997. Gender (SEX) had an odds ratio of .916 based on the female gender coded as female = 2 (Table 16). Overall, the logistic regression model was statistically significant, $X^2(4) = 10.028\, p < .05$ for the AD model and not statistically significant for the elevated amyloid model $X^2(4) = 6.790\, p > .05$.

Table 15

Variables in the Equation for AD

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	SEX	-.189	.116	2.664	1	.103	.828	.660	1.039
	SMOKYRS	-.007	.005	2.149	1	.143	.993	.984	1.002
	ALCOHOL	-.302	.156	3.755	1	.053	.739	.545	1.003
	NACCAANX	.179	.158	1.293	1	.256	1.196	.878	1.629
	Constant	.344	.195	3.127	1	.077	1.411		

a. Variable(s) entered on step 1: SEX, SMOKYRS, ALCOHOL, NACCAANX.

Table 16

Variables in the Equation for AB

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	SEX	-.088	.116	.574	1	.449	.916	.731	1.149
	SMOKYRS	-.003	.005	.482	1	.488	.997	.988	1.006
	ALCOHOL	-.353	.159	4.943	1	.026	.703	.515	.959
	NACCAANX	.090	.157	.326	1	.568	1.094	.804	1.488
	Constant	.136	.194	.488	1	.485	1.145		

a. Variable(s) entered on step 1: SEX, SMOKYRS, ALCOHOL, NACCAANX.

Discussion

Potential risk factors associated with Alzheimer's disease were quantifiably analyzed to identify levels of association between participant's cardiovascular events and an AD diagnosis. The postulation and framework that a positive correlation between behavioral factors and AD indicate a need to evaluate modifiable risk factors as a potential protective intervention to improve early AD and elevated amyloid detection (Finch & Kulminski, 2019; Larsson et al., 2017). Recognizing risk and the levels of association as a means of early AD detection can provide insight to healthcare providers aiming to diagnose and treat patients earlier before the disease progresses. The creation of early intervention may enhance patient and family members' quality of life in many respects when healthcare providers and patients are aware of associated risks and how to enhance people's quality of life both physically and economically.

Interpretation

The overall AD model was statistically significant. However, the individual components were not. The overall elevated amyloid model was not statistically significant. However, one variable, the presence of alcohol abuse (ALCOHOL), was (i.e., $p < .05$). Regardless of significance, the model highlights a positive and negative association between modifiable behavior (i.e., alcohol abuse, years of cigarette use, and current use of an anxiolytic, sedative, or hypnotic agent). Combining the independent variables improves predicting the potential diagnosis of AD seen in the Omnibus Tests of Model Coefficients significance. The odds ratio indicates that patients that use an anxiolytic, sedative, or hypnotic agent (NACCAANX) at 1.196, could be at an increased risk of AD. However, smoking history (SMOKYRS) at .993 and alcohol abuse (ALCOHOL) at .739 does not significantly impact an AD diagnosis.

The association level between alcohol abuse and an AD diagnosis indicates a negative correlation for the selected participants in this study. Participants with a history of alcohol abuse were less likely to have an AD diagnosis. There were similar findings with elevated amyloid with positive correlations with the use of an anxiolytic, sedative, or hypnotic agent and almost no correlations between elevated amyloid and having a smoking history. Chen et al. (2021) found that cigarette smoking was not associated with CSF Aβ42, t-tau, or p-tau levels over time in participants with mild cognitive impairment. They did find that cigarette smoking was associated with faster cognitive decline/function and could be a risk factor to consider when screening for AD. One significant finding for elevated amyloid was that the analysis indicated alcohol abuse

(ALCOHOL) at Exp(B) = .703, and $p < .05$ was not a risk factor. Larsson et al. (2017) indicate that frequent alcohol consumption could be a risk factor for AD and dementia. However, limited alcohol use was similar to abstaining from alcohol and found not to be associated with dementia. The research in this manuscript could provide evidence that there is a need to monitor patients more closely for early cognitive decline and AD when patients report behavioral risk factors. Smoking, heavy alcohol use, and anxiolytic, sedative, or hypnotic agents were insignificant for AD. There was a significant negative correlation between alcohol abuse and elevated amyloid, which appears counterintuitive based on the literature review. Regardless of this study's findings with selected participants, this manuscript as a whole indicates that monitoring patients for behavioral risk factors may improve AD diagnosis and health outcomes.

Limitations

The primary limitation in this study is the lack of participants assessed for tau proteins via a PET scan. Limiting co-variates and providing additional age limits may increase power in future studies. Simon (2021) indicates an association between tau proteins' formation, modifiable behavioral risk factors, and AD presence. The author indicates that modifiable behavioral risk factors account for 35% to 45% of AD risk and that tau depositions are associated with neuropsychiatric symptoms (NPSs), commonly found in patients with dementia. Additional limitations include spatial analysis that would provide a more comprehensive look at patients’ location and potential increases in exposure to environmental risk factors associated with AD. The National Alzheimer’s

Coordinating Center UDS does not include patients' location and is a limitation for understanding where clusters occur and additional behavioral risk factors.

Implications

This study potentially promotes social change by contributing to the knowledge surrounding risk and protective factors associated with AD. As people live longer and more people are diagnosed with AD, there is a need to identify early potential risk factors for creating interventions and therapies to decrease the progression of cognitive decline and burden on individuals and society (National Institute on Ageing [NIH], 2017). Based on the literature review, there are clear correlations between modifiable behavioral risk factors that provide health care providers regarding the potential of AD development (Finch & Kulminski, 2019). This study supports using current and pre-existing modifiable behavioral risk factors as indicators for assessing patients for cognitive decline over the age of 55. Although there is only one significant correlation in this study's model, the results show levels of association between modifiable behavioral risk factors variables. Implementing screening for cognitive health and AD when behavioral risk factors are present could be a novel way of influencing the monitoring and pre-diagnosis of AD.

This study provides implications for early AD detection. It contributes to an understanding that there is a need for action on the part of health care providers and patients regarding the promotion of detection and intervention of AD. There is a gap in knowledge concerning the exact determinants of health associated with the onset and presence of AD (Tini et al., 2020). The participants in this study are unique as the random

selection and associated variables have not previously been tested together, providing a novel assessment of the level of correlation between modifiable behavioral risk factors and the potential for AD diagnosis. Finch and Kulminski (2019) indicated a need for understanding what risk factors influence AD and content that there is an amalgamation of physical and environmental exposures that contribute to the disease. There is a need to continue to explore potential risk factors to more precisely identify the underlying mechanisms of AD to decrease the burden of the disease at the individual and societal level and promote positive social change.

Recommendations

There is a need for future studies to examine the effects of modifiable behavioral risk factors and AD outcomes. Modifiable behavior such as physical activity, illicit drug use, and diet are all known to influence health outcomes. Social demographic variables are also not assessed in this study. Race and ethnicity, educational levels, and economic status should be considered for future studies to identify behavior risk factors within communities, especially those with known inequality and inequity (Lourenco et al., 2018). Including sociodemographic variables in the model could increase the ability of healthcare providers to identify the risk for AD and provide therapeutic interventions before the disease progresses.

Additional recommendations include using other statistical analyses such as linear regression, which uses continuous variables to predict a possible AD outcome. According to Laerd Statistics (2022), a simple linear regression applies two variables to determine an outcome for a dependent variable. Instead of having a complete bivariate model, the

linear regression could independently assess the relationship between continuous variables and levels of cognitive decline rather than have yes or no outcomes. The limitation is the lack of information associated with the levels of cognitive decline, which is an additional consideration/recommendation for collecting data that measures the level of cognitive impairment from participants.

Conclusion

Alzheimer's disease is a growing epidemic and is the sixth-leading cause of death in the United States. Individuals with AD often have comorbidities due to the aging process, with cardiovascular health hypothesized as correlating with the development of the disease. Participants provided health information collected in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). The data included questions about the participant's current modifiable behaviors, an AD diagnosis, and elevated amyloid on a PET. A random selection of (n = 1,229) participants included (n = 611) not diagnosed with AD and (n=618) who were diagnosed with AD. Participants also include (n = 625) not diagnosed with elevated amyloid and (n = 604) who were diagnosed with elevated amyloid. A bivariate linear regression was conducted to identify the level of association between modifiable behavior variables and an AD diagnosis and elevated amyloid PET. The overall AD model found the combined modifiable health variables and an AD diagnosis significance. However, the second overall model for elevated amyloid PET and modifiable health variables was insignificant. Levels of association measured with an odds ratio indicate positive correlations between the current reported use of an anxiolytic, sedative, or hypnotic agent and a negative correlation for

years of smoked cigarettes and alcohol abuse regarding elevated amyloid PET and an AD diagnosis. Future research is needed to identify the association between additional modifiable health variables to improve the understanding of the behavioral health risks and the presence of amyloid-beta plaques and AD diagnosis.

References

Amakiri, N., Kubosumi, A., Tran, J, & Reddy, P. (2019). Amyloid-Beta and MicroRNAs in Alzheimer's Disease. *Frontiers in Neuroscience*, 13. https://doi.org/10.3389/fnins.2019.00430

Anderson, S. F., Kelley, K., & Maxwell, S. E. (2017). Sample-size planning for more accurate statistical power: A method adjusting sample effect sizes for publication bias and uncertainty. *Psychological Science, 28*(11), 1547–1562. https://doi.org/10.1177/0956797617723724

Bauer, E. A. (2018). The Impact of Frequently Used Antihistamines on Memory in Behaviorally Trained Caenorhabditis elegans. Doi: doi: 10.1067/mai.2000.106153

Caldwell, J. Z. K., Berg, J.-L., Cummings, J. L., & Banks, S. J. (2017). Moderating effects of sex on the impact of diagnosis and amyloid positivity on verbal memory and hippocampal volume. *Alzheimer's Research & Therapy, 9*, 1–10. doi: 10.1186/s13195-017-0300-8

Chen, M., Hu, C., Dong, H., Yan, H., Wu, P., & Alzheimer's Disease Neuroimaging Initiative (2021). A history of cigarette smoking is associated with faster functional decline and reduction of entorhinal cortex volume in mild cognitive impairment. *Aging, 13*(4), 6205–6213. https://doi.org/10.18632/aging.202646

Finch, C. E., & Kulminski, A. M. (2019). The Alzheimer's Disease Exposome. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 15*(9), 1123–1132. https://doi.org/10.1016/j.jalz.2019.06.3914

G*Power 3.1 Manual. (2021). General psychology and industrial psychology. Technical Manual. https://www.psychologie.hhu.de/fileadmin/redaktion/Fakultaeten/Mathematisch-Naturwissenschaftliche_Fakultaet/Psychologie/AAP/gpower/GPowerManual.pdf

Kawase, A., Chuma, T., Irie, K., Kazaoka, A., Kakuno, A., Matsuda, N., Shimada, H., & Iwaki, M. (2021). Increased penetration of diphenhydramine in brain via proton-coupled organic cation antiporter in rats with lipopolysaccharide-induced inflammation. Brain, Behavior, & Immunity - *Health*, 10. https://doi.org/10.1016/j.bbih.2020.100188

Laerd Statistics. (2022). Binomial Logistic Regression. Retrieved from https://statistics.laerd.com/premium/index.php

Langballe, E. M., Ask, H., Holmen, J., Stordal, E., Saltvedt, I., Selbæk, G., Fikseaunet, A., Bergh, S., Nafstad, P., & Tambs, K. (2015). Alcohol consumption and risk of dementia up to 27 years later in a large, population-based sample: the HUNT study, Norway. *European Journal of Epidemiology*, *30*(9), 1049-1056. https://doi.org/10.1007/s10654-015-0029-2

Larsson, S. C., Traylor, M., Malik, R., Dichgans, M., Burgess, S., & Markus, H. S. (2017). Modifiable pathways in Alzheimer's disease: Mendelian randomization analysis. BMJ: British Medical Journal, 359.

National Alzheimer's Coordinating Center (2021). Description of the NACC database. Retrieved from https://www.alz.washington.edu/WEB/data_descript.html

Simon, S. S. (2021). Good news for dementia prevention: Multiple behavioral features are associated with markers of brain pathology in the preclinical phase of sporadic and autosomal dominant Alzheimer's disease. Biological Psychiatry, 89(8), 739–741. https://doi.org/10.1016/j.biopsych.2021.02.001

Tachibana, M., Holm, M., Liu, C., Shinohara, M., Aikawa, T., Oue, H., Yamazaki, Y., Martens, Y., Murray, M., Sullivan, P., Weyer, K., Glerup, S., Dickson, D., Bu, G., Kanekiyo T. (2019). APOE4-mediated amyloid-β pathology depends on its neuronal receptor LRP1. J Clin Invest, *1;129*(3):1272-1277. doi: 10.1172/JCI124853. Epub 2019 Feb 11. PMID: 30741718; PMCID: PMC6391135.

Wong, H. (2015). Long-term use of diphenhydramine. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, *187*(14), 1078. https://doi.org/10.1503/cmaj.1150066

Zheng, Y.-B., Shi, L., Zhu, X.-M., Bao, Y.-P., Bai, L.-J., Li, J.-Q., Liu, J.-J., Han, Y., Shi, J., & Lu, L. (2021). Anticholinergic drugs and the risk of dementia: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, *127*, 296–306. https://doi.org/10.1016/j.neubiorev.2021.04.031

Social Interaction and Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a growing epidemic and is the sixth-leading cause of death in the United States. Individuals with AD often have comorbidities due to the aging process. There is a lack of research on comorbidities as associated risk factors for AD. One of the leading hypotheses contends there are correlations between living situations, personal care, community engagement, and risk for AD and amyloid-beta plaques (Seaman, 2021). This study is guided by Finch and Kulminski's (2019) AD Exposome as a caveat to explore a patient's environment (i.e., staying at home rather than doing new activities, dropping activities and interests, and the participant's level of independence), an AD diagnosis, and elevated amyloid-beta plaques. Participants provided health information collected in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). A random selection of (n = 1,229) participants included (n = 737) not diagnosed with AD and (n = 492) who were diagnosed with AD. Participants also include (n = 699) not diagnosed with elevated amyloid and (n=530) who were diagnosed with elevated amyloid. A bivariate linear regression was conducted to identify the level of association between social isolation risk factors and an AD diagnosis and elevated amyloid PET. The overall AD and elevated amyloid were significant. Levels of association measured with an odds ratio indicate positive correlations between the reported participant's level of independence regarding elevated amyloid PET and an AD diagnosis. Future research is needed to identify the association between additional modifiable health variables to improve the understanding of the social isolation risk factors and the presence of amyloid-beta plaques and AD diagnosis.

Introduction

Alzheimer's disease is a growing epidemic and is the sixth-leading cause of death in the United States, with diagnoses expected to triple by 2060 to over 14 million people (CDC, 2020). Individuals with AD often have lifestyle risk factors in concert with the aging process. Evidence of a trifecta between physical health, behavior, and psychological welfare are considered risk factors for AD. Living situations, personal care, and engagement with one's community profoundly affect neurological and cognitive health (Seaman, 2021). Salinas et al. (2021) examined a cohort of participants 45 years and older to identify the impacts of loneliness and isolation and the presence of dementia and AD. The authors found a significant association between a lack of social support and lower cognitive function. The authors found that social support, isolation, lower listener availability, and overall presence/availability of social interaction are vital to mental and cognitive health.

Social isolation and a lack of community engagement are risk factors for mental decline due to a lack of stimuli in the brain and the potential for abnormal Aβ plaque buildup (Prodo Lima et al., 2018). Researching environmental engagement and social isolation levels is necessary to understand specific associated risk and protective factors (Salinas et al., 2021; Seaman, 2018). Correlations between an AD diagnosis and the presence of abnormal Aβ plaque concerning modifiable behavior such as exercise, social enrichment, and isolation are unclear. Improving the understanding of the level of association between risk factors and the presence of cognitive decline and Aβ plaque will provide healthcare providers with more information needed to create AD interventions.

Significance

As people live longer due to healthcare, technology, and equity improvements, research needs to identify risk factors associated with AD. AD is unique in the older adult population, and it is vital to managing expected increases in the disease over the next 40 years (Finch et al., 2019). This study provides original statistical data and quantitative analysis that examines the physiological and psychological approach to AD research by assessing the relationship between environmental engagement factors health and an AD diagnosis/Aβ plaques. Environmental risk and association research increase the potential to create interventions, especially in vulnerable communities, and promote positive social change (Salinas et al., 2021). Altering behavior to promote healthy longevity impacts individuals and encourages social well-being by lessening the burden of AD on families, communities, and health resources (Nguyen et al., 2018). A limited number of studies address the specific level of relationship between social isolation, environmental engagement, and the presence of AD and Aβ deposits.

This study's theoretical framework applies Finch and Kulminski's (2019) AD exposome and Bronfenbrenner's (1977) ecological systems theory (EST) theoretical framework. Finch and Kulminski's (2019) AD Exposome is used as a guide to explore a patient's environmental risk factors and an AD diagnosis. The hypothesis for this study uses the AD Exposome and Bronfenbrenner's EST to guide the thought process of associating social isolation, levels of community engagement, and environmental enrichment as potential risk factors with cognitive decline and developing AD. Bronfenbrenner's (1977) ecological systems theory theoretical framework works with

Finch and Kulminski's (2019) AD exposome by suggesting a person's environment affects lifestyle choices and health outcomes. The two theories work together as a framework for this study and provide a means to study correlations between environmental risk factors and associations with Aβ plaques and AD.

There is no clear understanding of the level of environmental risk concerning the early onset of AD and cognitive decline. Finch and Kulminski (2019) explained that environmental and environmental risk factors contribute to AD aging, indicating that brain aging and cognitive decline are vulnerable to multiple variables. The authors look at numerous environmental factors and indicate that ApoE4, a gene that influences the production of a protein called apolipoprotein E, increases the risk of late-onset AD and the amount of amyloid-β (Aβ) peptides in the brain (Finch & Kulminski, 2019). The authors proposed a need for more research focusing on extraneous factors beyond genetics to understand AD risk better. Environmental risk factors such as social isolation and physical engagement in one's surroundings may affect cognitive decline and AD diagnosis by promoting the presence of Aβ plaques biomarkers associated with AD. The extent of such environmental risk factors is in question and suggests a need to research levels associated with AD diagnosis to determine the benefits of social and societal interventions.

Relevant Scholarship

Social interaction and environmental engagement have varying effects on social determinants of health and health outcomes. Seaman (2018) indicated numerous negative impacts on health outcomes and the progression of AD when a person's lack of care and

environmental engagement increases pre and post-AD diagnosis. The author conducted a 26-month ethnographic study of participants with early onset of AD, their families, and healthcare providers. Qualitative analysis found that participants who had regular interactions with family and lived in social environments that supported conversation and engaging activities were much better than those in isolation or living in care facilities that did not promote regular engagement. Similarly, Salinas et al. (2021) conducted a retrospective cross-sectional analysis examining cognitive function and resilience in addition to AD. The authors found that five types of social support, such as supportive listening and environmental engagement, contributed to enhanced cognitive function and resilience.

Social isolation and a lack of community engagement are risk factors for mental decline and increase the potential for AD and abnormal Aβ plaque buildup. Prodo Lima et al., 2018 studied the significance of environmental enrichment (EE) as a neuroprotective strategy. Ali et al. (2017) indicate that AD is a neurogenerative disease associated with memory loss. The authors conducted a study identifying correlations between social isolation as a risk factor for AD in rats. They found that rats in isolation had elevated Aβ plaque buildup in the brain compared to those not in isolation over a long period. The authors suggest that social isolation and a lack of environmental engagement may aid in identifying the presence and severity of AD and provide advice for additional research in other communities.

Bagheri (2018) indicates a need to think spatially about community environments to identify populations where isolative living situations occur to improve interventions

that promote interaction for communities at risk for AD based on available demographic and census data. This thinking is beneficial because it promotes research regarding where and how people interact with their environment and identify protective factors. Prodo Lima et al., 2018 indicate that environmental enrichment (EE), such as increased physical activity and social interaction, directly affects a person's risk for developing AD. The authors found that injections of Aβ plaque proteins in animals, a cause of oxidative stress and memory impairment, are less burdensome in subjects exposed to EE and suggest that physical activity and social interaction are critical protective factors that help prevent AD.

Like other animals, social interaction is vital for humans and provides mental and physical support that enhances social determinants of health and health outcomes. Spreng and Bzdok (2021) recently researched the effects of isolation stemming from the COVD-19 pandemic on elderly participants. They found that loneliness and isolation directly affect physical and mental health and enhance AD risk in older populations. The authors indicate a critical need to understand the detriments that social isolation causes in humans and how it affects the human brain and cognitive decline. Han et al. (2019) add to the conversation by explicitly stating the need for epidemiological interventions (e.g., environmental, social, and physical) to improve older adults' longevity and quality of life. They suggest that epidemiologic studies such as those that study the connection between environmental exposures and AD development are needed to identify external influences to improve health outcomes.

Research Question

What is the association level between living situations and interests in social activities concerning amyloid-β plaques proteins and an AD diagnosis in participants between 55 and 80 years of age, controlling for age and other confounders?

Nature of the Study and Design

I used a quantitative approach to analyze the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) to explore the effects of social activities and the presence of amyloid-β plaques/tau proteins in an AD diagnosis. For this study, the independent variables were social isolation risk factors (i.e., staying at home rather than doing new activities, dropping activities and interests, and type of residence). The dependent variable is the presence of amyloid-β plaques/tau proteins and an AD diagnosis. The results intend to aid healthcare providers' understanding of the level of association between environmental risk factors and cognitive decline.

Methods

Population

The target population for this study is a cohort of participants in the NACC's UDS who have varying cognitive impairment levels. Study participants have diverse demographic backgrounds, and those considered cognitively normal participate in the study as a control (National Alzheimer's Coordinating Center, 2021). The Alzheimer's Disease Research Centers (ADRCs) collect across the United States from 37 locations.

Sample and Power

Stratified random sampling was used in this study while controlling for age. Participants under 55 were excluded due to the lack of AD prevalence in younger populations Lourenco et al. (2018). The study does not discriminate between those with or without cognitive decline. Only participants who have completed surveys for the modifiable behavior (i.e., staying at home rather than doing new activities, dropping activities and interests, and type of residence) were included.

The power levels for this analysis were based on $\delta = 0.3$, $\delta = 0.5$, and $\delta = 0.8$, which is consistent with Cohen's small, medium, and large effect sizes. The effect size ensures the rejection of a false null hypothesis or Type 1 error (Anderson et al., 2017). G* Power Statistics 3.1 was used to calculate appropriate sample sizes guided by the G*Power Statistics Manual (2021). The selected statistical test is Logistic Regression, and the type of power analysis was "A priori." The effect size input mode will be "Two Probabilities," which is the probability of an event under H_0 and H_1, in terms of p_1 and p_2, which is a two-tailed test, $\Pr(Y = 1 \mid X = 1)\, H1 = 0.1$ and $\Pr(Y = 1 \mid X = 1)\, H0 = 0.05$. An alpha ($\alpha$) level of 0.05 was used to reject or accept the null hypothesis. The significance level $\alpha = 0.05$ indicates a 5% probability of type I error where the null hypothesis is incorrectly rejected (Anderson, 2017). The last input includes *Power (1-β err prob):* 0.95, R^2 other X: 0, X Distribution: Binomial, and *X parm π: 0.5* to generate a sample size needed to achieve reliable results (G*Power 3.1 Manual, 2021). The total sample size for logistic regression is a *Critical z:* 1.95996, *Total samples size:* $N = 1299$, and *Actual power:* 0.950068.

Sources of Data

The study used a quantitative approach. It involved using publicly available National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and census data from the United States Census Bureau 2020. The data is de-identified and contains a systematic random sampling of participants.

Instrumentation

Data was requested through the National Alzheimer's Coordinating Center (NACC). And it requires a detailed report outlining the purpose and intentions for the data's use. The NACC provided an SPSS Investigator NACC sav. file for analysis (NACC, 2021). The data in the UDS includes information concerning demographics (e.g., sex and year of birth), staying at home preference, dropping activities of interest, and level of independence, abnormally elevated amyloid on PET, tau PET evidence for AD, and presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease (Table 1). Variable type codes include female/male and year for demographics; all others were recorded as 0 = Absent and 1= Recent/Active except for the level of independence on a scale of 1-4. Patients with codes 9 and -4 unknown were not included in this study.

Table 1

NACC UDS Researcher's Data Dictionary Derived Variables

Form	Variable Name	Short Descriptor	Variable Type	Allowable Codes	Source
A1 Subject Demographics	BIRTHYR	Subject's year of birth	Original UDS question	1875 to (current year minus 15)	v1-3
A1 Subject Demographics question	SEX	Subject's sex	Original UDS	1=Male 2=Female	v1-3
B6 Geriatric Depression Scale (GDS) ST	STAYHOME	Do you prefer to stay at home, rather than going out and doing new things?	Original UDS question	0 = No 1 = Yes 9 = Did not answer -4 = Not available: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v1-3
B6 Geriatric Depression Scale (GDS)	DROPACT	Have you dropped many of your activities and interests?	Original UDS question	0 = No 1 = Yes 9 = Did not answer -4 = Not available: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v1-3

A1 Subject Demographics	INDEPEND	Level of independence	Original UDS question	1=Able to live independently 2=Requires some assistance with complex activities 3=Requires some assistance with basic activities 4=Completely dependent 9=Unknown	v1-3
D1 Clinician Diagnosis	AMYLPET	Abnormally elevated amyloid on PET	Original UDS question	0 = No 1 = Yes 8 = Unknown/not assessed -4 = Not applicable: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v3
D1 Clinician Diagnosis	TAUPETAD	Tau PET evidence for AD	Original UDS question	0 = No 1 = Yes 8 = Unknown/not assessed -4 = Not applicable: UDS form submitted did not collect data in this way, or a skip pattern precludes response to this question	v3

D1 Clinician Diagnosis	NACCALZD	Presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease	NACC derived variable	0 = No (assumed assessed and found not present) 1 = Yes 8 = No cognitive impairment	v1-3

Design Analysis

The quantitative analysis identifies links between social isolation risk factors, amyloid-β plaques/tau proteins, and AD diagnosis. Bivariate logistic regression, Omnibus Tests of Model Coefficients, and Cox and Snell's /Nagelkerke's was used to test overall statistical significance and the strength of association between variables. IBM Statistical Package for Social Sciences (SPSS) 27 was used to determine an odds ratio output (i.e., β-values) between dependent and independent variables and answer the following research questions:

Research Question: Based on the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), what are the association levels between staying at home rather than doing new activities, dropping activities and interests, and level of independence, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants who are between the ages of 55 and 80 years of age controlling for age and other confounders?

$H_0$1: Based on the NACC Uniform Data Set, there are no associations between staying at home rather than doing new activities, dropping activities and interests, level of

independence, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

H_a1: Based on the NACC Uniform Data Set, there are associations between staying at home rather than doing new activities, dropping activities and interests, level of independence, amyloid-β plaques/tau proteins, and the risk of developing Alzheimer's disease in participants between 55 and 80 years of age.

The data were screened for missing, unknown, and outlying data. The chosen statistical test is a binary logistic regression, and the statistical significance level is $\alpha = 0.05$. A binary logistic regression is applicable when testing the outcome of a dichotomous variable (i.e., presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease). Testing for assumptions was conducted before running the regression. According to Laerd Statistics (2022), assumptions include a dichotomous dependent variable, contentious or nominal independent variables, independence between the observations, a minimum number of participants, linearity between the independent and dependent variables, independence, no multicollinearity, and no significant outliers. The rationale for selecting the covariates age and gender stems from Cladwell et al. (2017), who indicate age and gender influence AD biomarkers.

Results

Execution

Once I received Institutional Review Board approval, study #03-10-22-0978803, I completed the required data request through the National Alzheimer's Coordinating Center (NACC). After contacting the NACC and providing a detailed report outlining the

purpose and intentions for the data's use, they provided an SPSS Investigator NACC sav. file for analysis (NACC, 2021). The total number of participants included in the data set was 164,265.

The G* Power Statistics calculated prior to the data collection applied sample sizes guided by the G*Power Statistics Manual (2021). The selected statistical test was Logistic Regression, and the effect size input mode was "Two Probabilities," which is the probability

of an event under H_0 and H_1, in terms of p_1 and p_2, which is a two-tailed test, $\Pr(Y = 1 \mid X = 1)\, H1 = 0.1$ and $\Pr(Y = 1 \mid X = 1)\, H0 = 0.05$. An alpha (α) level of 0.05 was used to reject or accept the null hypothesis. The significance level α = 0.05 indicates a 5% probability of type I error where the null hypothesis is incorrectly rejected (Anderson, 2017). The last input included *Power (1-β err prob):* 0.95, R^2 other X: 0, X Distribution: Binomial, and *X parm π: 0.5* to generate a sample size needed to achieve reliable results (G*Power 3.1 Manual, 2021).

The total sample size for logistic regression is a *Critical z:* 1.95996, *Total samples size:* $N = 1229$, and *Actual power:* 0.950068 for the dependent variables AMYLPET (Abnormally elevated amyloid on PET) and NACCALZD (Presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease). Due to the lack of participants who received testing for the dependent variable TAUPETAD (Tau PET evidence for AD), the variable is not used in the study as there is not enough power to provide results avoiding a type I or type II error. All independent variables are present in the analysis for the 1,229 randomly selected participants.

Results

The total sample size from the NACC Uniform Data Set is 1,229 participants (Table 2). Participants include only those assessed for the presumptive etiologic diagnosis of the cognitive disorder — Alzheimer's disease and abnormally elevated amyloid on PET are the dependent variables. The independent variables are staying at home rather than doing new activities, dropping activities and interests, and level of independence. As previously stated, excluded participants are those assessed for tau PET evidence for AD due to a low rate of tau assessment. The dependent variable was re-coded as 0 = No AD and 1 = Yes AD (Table 3) and 0 = No AB and 1 = Yes AB (Table 4). The model includes the constant without adding the independent variables for AD (Table 5) and abnormally elevated amyloid on PET (Table 6). The classification table assumes that all participants have AD or elevated amyloid, and the model only correctly classified cases 60.0% of the time for AD and 56.9% for elevated amyloid (Laerd Statistics, 2022). After selecting the sample size, I tested assumptions per Laerd Statistics (2022). Assumptions met the requirements of a dichotomous dependent variable, contentious or nominal independent variables, independence between the observations, a minimum number of participants, linearity between the independent and dependent variables, independence, no multicollinearity, and no significant outliers.

Table 2

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	1229	100.0
	Missing Cases	0	.0
	Total	1229	100.0
Unselected Cases		0	.0
Total		1229	100.0

a. If weight is in effect, see classification table for the total number of cases.

Table 3

Dependent Variable Encoding

Original Value	Internal Value
No AD	0
Yes AD	1

Table 4

Dependent Variable Encoding

Original Value	Internal Value
No AB	0
Yes AB	1

Table 5

Classification Table[a,b]

			Predicted		
			NACCALZD		Percentage
	Observed		No AD	Yes AD	Correct
Step 0	NACCALZD	No AD	0	737	100.0
		Yes AD	0	492	.0
	Overall Percentage				60.0

a. Constant is included in the model.

b. The cut value is .500

Table 6

Classification Table[a,b]

			Predicted		
			AMYLPET		Percentage
	Observed		No AB	Yes AB	Correct
Step 0	AMYLPET	No AB	699	0	100.0
		Yes AB	530	0	.0
	Overall Percentage				56.9

a. Constant is included in the model.

b. The cut value is .500

Data Analysis

Three tests were used to identify the model fit for the use of bivariate logistic regression for both dependent variables AD diagnosis and elevated amyloid. The Omnibus Tests of Model Coefficients indicate the overall significance of the model (Laerd Statistics, 2021). The results show that the model is significant (i.e., $p < .05$), meaning the model is a good fit for the use of bivariate logistic regression for AD

diagnosis and abnormally elevated amyloid-beta (Tables 7 and 8). The Hosmer and Lemeshow goodness of fit test indicate that the model for the presence of AD may be a poor fit, with a $p < 0.001$ (Table 9). However, the model for abnormally elevated amyloid-beta is not a poor fit as it is not significantly poor, with a $p = .74$ or $p > .05$ (Table 10). Lastly, I ran a Model Summary with Cox & Snell R Square and Nagelkerke R Square values (Laerd Statistics, 2021). The results indicate that the explained variation in the dependent variable ranges from 28.0% for Cox & Snell R Square values and 37.9% for Nagelkerke R Square values for an AD diagnosis (Table 11). Elevated amyloid results range from 16.3% for Cox & Snell R Square values and 21.8% for Nagelkerke R Square values (Table 12).

Since bivariate logistic regression is a way to estimate the probability of an event occurring, I created a classification table to assess the model's effectiveness. It is common to use logistic regression to predict outcomes based on independent variables (Laerd Statistics, 2022). The cut value is .500, indicating that the probability of classifying a yes AD value is greater than .500. Previously, the classification table without the independent variables (Tables 5 and 6) showed that only 60.0% and 56.9% of cases would correctly be classified by assuming that cases were yes AD and no AB. Including the independent variables in the model enhances the ability to classify a patient’s probability of having or not having AD or AB to 79.9% for AD and 71.1% of cases for AB (Tables 13 and 14).

Table 7

Omnibus Tests of Model Coefficients for AD

		Chi-square	df	Sig.
Step 1	Step	404.064	4	<.001
	Block	404.064	4	<.001
	Model	404.064	4	<.001

Table 8

Omnibus Tests of Model Coefficients for AB

		Chi-square	df	Sig.
Step 1	Step	218.021	4	<.001
	Block	218.021	4	<.001
	Model	218.021	4	<.001

Table 9

Hosmer and Lemeshow Test for AD

Step	Chi-square	df	Sig.
1	40.001	6	<.001

Table 10

Hosmer and Lemeshow Test for AB

Step	Chi-square	df	Sig.
1	11.516	6	0.74

Table 11

Model Summary AD

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	1250.523[a]	.280	.379

b. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Table 12

Model Summary AB

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	1462.422[a]	.163	.218

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Table 13

Classification Table[a] for AD

			Predicted NACCALZD		Percentage
	Observed		No AD	Yes AD	Correct
Step 1	NACCALZD	No AD	662	75	89.8
		Yes AD	172	320	65.0
	Overall Percentage				79.9

a. The cut value is .500

Table 14

Classification Table[a] for AB

			Predicted		
			NACCALZD		Percentage
	Observed		No AD	Yes AD	Correct
Step 1	AMYLPET	No AB	589	110	84.3
		Yes AB	245	285	53.8
	Overall Percentage				71.1

a. The cut value is .500

Findings

Bivariate logistic regression in SPSS produced a “Variables in the Equation” table that indicates the level of contribution each independent variable has in the model and their statistical significance (Laerd Statistics, 2022). The Wald test provides the significance of each variable to the model. None of the variables are significant regarding correlations between modifiable risk factors and an AD diagnosis (Table 15). The same was found for elevated amyloid, except for the independent variable alcohol abuse. The odds ratio or "Exp(B)" column, along with confidence intervals (i.e., 95% C.I.), indicates the change in the odds for each increase in one unit of the independent variable (Laerd Statistics, 2022). The results for the presence of an AD diagnosis non-significant odds ratios for staying at home rather than doing new activities (STAYHOME) with Exp(B) = .810 and dropping activities and interests (DROPACT) at Exp(B) = 1.094. The results for a participant’s level of independence (INDEPEND) were significant at $p < .001$ and Exp(B) = 8.733. Similarly, elevated amyloid shows non-significant odds ratios for dropping activities and interests (DROPACT) at Exp(B) = .781. The results for a

participant's level of independence (INDEPEND) were significant at $p < .001$ with Exp(B) = 4.073 and staying at home rather than doing new activities (STAYHOME) with Exp(B) = .731 with $p < .05$. Gender (SEX) had an odds ratio of 1.080 for AD and 1.041 for AB based on the female gender coded as female = 2 (Table 16). Overall, the logistic regression model was statistically significant, $X^2(4) = 404.064\ p < .001$ for the AD model and the elevated amyloid model $X^2(4) = 218.021\ p > .001$.

Table 15

Variables in the Equation for AD

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	SEX	.077	.143	.289	1	.591	1.080	.816	1.428
	STAYHOME	-.211	.171	1.513	1	.219	.810	.579	1.133
	DROPACT	.090	.190	.225	1	.635	1.094	.754	1.587
	INDEPEND	2.167	.139	244.75	1	<.001	8.733	6.657	11.457
	Constant	-3.527	.318	122.67	1	<.001	.029		

a. Variable(s) entered on step 1: SEX, STAYHOME, DROPACT, INDEPEND.

Table 16

Variables in the Equation for AB

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	SEX	.040	.128	.098	1	.754	1.041	.810	1.339
	STAYHOME	-.313	.155	4.082	1	.043	.731	.539	.991
	DROPACT	-.247	.175	1.984	1	.159	.781	.554	1.101
	INDEPEND	1.404	.112	157.36	1	<.001	4.073	3.270	5.072
	Constant	-2.205	.274	64.900	1	<.001	.110		

a. Variable(s) entered on step 1: SEX, STAYHOME, DROPACT, INDEPEND.

Discussion

Potential risk factors associated with Alzheimer's disease were quantifiably analyzed to identify levels of association between participant’s cardiovascular events and an AD diagnosis. The postulation and framework that a positive correlation between behavioral factors and AD indicate a need to evaluate modifiable risk factors as a potential protective intervention to improve early AD and elevated amyloid detection (Finch & Kulminski, 2019; Larsson et al., 2017). Recognizing risk and the levels of association as a means of early AD detection can provide insight to healthcare providers aiming to diagnose and treat patients earlier before the disease progresses. The creation of early intervention may enhance patient and family members’ quality of life in many respects when healthcare providers and patients are aware of associated risks and how to enhance people’s quality of life both physically and economically.

Interpretation

The overall AD and AB models were statistically significant. Although the individual variables staying at home rather than doing new activities and dropping activities and interests were not significant, they contributed to the overall model for AD diagnosis. Additionally, participants' level of independence and staying at home rather than doing new activities were independently significant for the presence of elevated amyloid. Regardless of significance, the model highlights a positive and negative association between modifiable behavior (i.e., staying at home rather than doing new activities, dropping activities and interests, and the participant's level of independence). Combining the independent variables improves predicting the potential diagnosis of AD seen in the Omnibus Tests of Model Coefficients significance. The odds ratio for staying at home rather than doing new activities (STAYHOME) with Exp(B) = .810 indicates a slight decrease for AD diagnosis and dropping activities and interests (DROPACT) at Exp(B) = 1.094 a slight increase for AD diagnosis, but independently not significant. However, the results for a participant's level of independence (INDEPEND) were significant at $p < .001$ and Exp(B) = 8.733 and indicate that independence is strongly associated with an AD diagnosis. The findings indicate that a less independent patient has an 8.7 times higher chance of having an AD diagnosis.

The results for a participant's level of independence (INDEPEND) were significant at $p < .001$ with Exp(B) = 4.073 and staying at home rather than doing new activities (STAYHOME) with Exp(B) = .731 with $p < .05$ for elevated amyloid. These findings indicate positive correlations between the independent variable of independence

and the presence of elevated amyloid, a know risk factor for AD. Participants who reported staying at home rather than doing new activities had a negative correlation with elevated amyloid, indicating a variable that may not be as much as an associated risk of concern. For AD diagnosis and elevated amyloid presence, a participant's level of independence is a primary concern and risk factor in this study. The research in this manuscript could provide evidence that there is a need to monitor patients more closely for early cognitive decline and AD when patients report social isolation and a lack of community engagement as risk factors. There was a significant positive correlation between participants' level of independence, AD, and elevated amyloid, which aligns with the literature review. Regardless of this study's findings with selected participants, this manuscript as a whole indicates that monitoring patients' social isolation and a lack of community engagement as risk factors may improve AD diagnosis and health outcomes.

Limitations

The primary limitation is this study that the lack of participants assessed for tau proteins via a PET scan. Limiting co-variates and age limits may increase the sample size and provide the same power in future studies. Prado Lima et al. (2018) indicate an association between tau proteins' formation and cognitive loss as a risk factor for AD. The authors indicate that an increase in social engagement and a person's environment, such as living in isolation or level of independence, correlates with the development of AD and possible cognitive issues. In other words, they found a positive correlation between social engagement and delaying AD development. Additional limitations include

spatial analysis that would provide a more comprehensive look at patients' location and potential increases in exposure to environmental risk factors associated with AD. The National Alzheimer's Coordinating Center UDS does not include patients' location and is a limitation for understanding where clusters occur and additional behavioral risk factors.

Implications

This study potentially promotes social change by contributing to the knowledge surrounding risk and protective factors associated with AD. As people live longer and more people are diagnosed with AD, there is a need to identify early potential risk factors for creating interventions and therapies to decrease the progression of cognitive decline and burden on individuals and society (National Institute on Ageing [NIH], 2017). Based on the literature review, there are correlations between social isolation risk factors that can provide health care providers regarding the potential for AD development (Drinkwater et al., 2021). This study supports using current and pre-existing social isolation risk factors as indicators for assessing patients for cognitive decline over the age of 55. There are three significant correlations in this study's model. The results show significant levels of correlation between staying at home rather than doing new activities and the participant's level of independence. Staying at home rather than doing new activities indicate a decreased risk for elevated amyloid. In contrast, the participant's level of independence indicates a significantly increased risk for an AD diagnosis and elevated amyloid. Implementing screening for cognitive health and AD when social isolation risk factors are present could be a novel way of influencing the monitoring and pre-diagnosis of AD.

This study provides implications for early AD detection. It contributes to an understanding that there is a need for action on the part of health care providers and patients regarding the promotion of detection and intervention of AD. There is a gap in knowledge concerning the exact determinants of health associated with the onset and presence of AD (Tini et al., 2020). The participants in this study are unique as the random selection, and associated variables have not previously been tested together, providing a novel assessment of the level of correlation between social isolation risk factors and the potential for AD diagnosis. Finch and Kulminski (2019) indicate a need for understanding what risk factors influence AD and content that there is an amalgamation of physical and environmental exposures that contribute to the disease. There is a need to continue to explore potential risk factors to more precisely identify the underlying mechanisms of AD to decrease the burden of the disease at the individual and societal level and promote positive social change.

Recommendations

There is a need for future studies to examine the effects of social isolation, environmental engagement, and the presence of AD and Aβ deposits. Risk factors such as staying at home rather than doing new activities, dropping activities and interests, and the participant's level of independence indicate risk factors that influence health outcomes found in the literature review. Social demographic variables are also not assessed in this study. Race and ethnicity, educational levels, and economic status should be considered for future studies to identify behavior risk factors within communities, especially those with known inequality and inequity (Lourenco et al., 2018). Including sociodemographic

variables in the model could increase the ability of healthcare providers to identify the risk for AD and provide therapeutic interventions before the disease progresses.

Additional recommendations include using other statistical analyses such as linear regression, which uses continuous variables to predict a possible AD outcome. According to Laerd Statistics (2022), a simple linear regression applies two variables to determine an outcome for a dependent variable. Instead of having a complete bivariate model, the linear regression could independently assess the relationship between continuous variables and levels of cognitive decline rather than have yes or no outcomes. The limitation is the lack of information associated with the levels of cognitive decline, which is an additional consideration/recommendation for collecting data that measures the level of cognitive impairment from participants.

Conclusion

Alzheimer's disease is a growing epidemic and is the sixth-leading cause of death in the United States. Individuals with AD often have comorbidities due to the aging process, with cardiovascular health hypothesized as correlating with the development of the disease. Participants provided health information collected in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). The data included questions about the participant's current social isolation risk factors, an AD diagnosis, and elevated amyloid on a PET. A random selection of (n = 1,229) participants included (n = 737) not diagnosed with AD and (n = 492) who were diagnosed with AD. Participants also include (n = 699) not diagnosed with elevated amyloid and (n = 530) who were diagnosed with elevated amyloid. A bivariate linear regression was conducted

to identify the level of association between current and pre-existing social isolation risk factors and an AD diagnosis and elevated amyloid PET. The overall AD model found the combined social isolation variables and an AD diagnosis significance. Levels of association measured with an odds ratio indicate positive correlations between the reported participant's level of independence regarding elevated amyloid PET and an AD diagnosis. Future research is needed to identify the association between additional modifiable health variables to improve the understanding of the social isolation risk factors and the presence of amyloid-beta plaques and AD diagnosis.

References

Ali, A.A., Khalil, M.G., Elariny, H.A., Abu-Elfotuh, K. (2017) Study on Social Isolation as a Risk Factor in Development of Alzheimer's Disease in Rats. Brain Disord Theory, *6*(2). https://doi: 10.4172/2168-975X.1000232

Anderson, S. F., Kelley, K., & Maxwell, S. E. (2017). Sample-size planning for more accurate statistical power: A method adjusting sample effect sizes for publication bias and uncertainty. *Psychological Science, 28*(11), 1547–1562. https://doi.org/10.1177/0956797617723724

Bagheri, N., Wangdi, K., Cherbuin, N., & Anstey, K.J. (2018). Combining Geospatial Analysis with Dementia Risk Utilising General Practice Data: A Systematic Review. *The Journal of Prevention of Alzheimer's Disease*, 5(1):71-77. https://doi.org/10.14283/jpad.2017.33

Bronfenbrenner, U. (1977). Toward an experimental ecology of human development. *American Psychologist, 32*(7), 513-531.

Caldwell, J. Z. K., Berg, J.-L., Cummings, J. L., & Banks, S. J. (2017). Moderating effects of sex

on the impact of diagnosis and amyloid positivity on verbal memory and hippocampal volume. *Alzheimer's Research & Therapy, 9,* 1–10. doi:10.1186/s13195-017-0300-8

Centers for Disease Control and Prevention [CDC] (2020). Alzheimer's Disease. https://www.cdc.gov/aging/aginginfo/alzheimers.htm

Finch, C. E., & Kulminski, A. M. (2019). The Alzheimer's Disease Exposome. *Alzheimer's & dementia: the journal of the Alzheimer's Association*, *15*(9), 1123–1132. https://doi.org/10.1016/j.jalz.2019.06.3914

G*Power 3.1 Manual. (2021). General psychology and industrial psychology. Technical Manual. https://www.psychologie.hhu.de/fileadmin/redaktion/Fakultaeten/Mathematisch-Naturwissenschaftliche_Fakultaet/Psychologie/AAP/gpower/GPowerManual.pdf

Han, L. K. M., Verhoeven, J. E., Tyrka, A. R., Penninx, B. W. J. H., Wolkowitz, O. M., Månsson, K. N. T., Lindqvist, D., Boks, M. P., Révész, D., Mellon, S. H., & Picard, M. (2019). Accelerating research on biological aging and mental health: Current challenges and future directions. Psychoneuroendocrinology, 106, 293–311. https://doi.org/10.1016/j.psyneuen.2019.04.004

Laerd Statistics. (2022). Binomial Logistic Regression. Retrieved from https://statistics.laerd.com/premium/index.php

Larsson, S. C., Traylor, M., Malik, R., Dichgans, M., Burgess, S., & Markus, H. S. (2017). Modifiable pathways in Alzheimer's disease: Mendelian randomization analysis. BMJ: British Medical Journal, 359.

Lourenco, J., Serrano, A., Santos-Silva, A., Gomes, M., Afonso, C., Freitas, P., Paul, C., & Costa, E. (2018). Cardiovascular Risk Factors are Correlated with Low Cognitive Function among Older Adults Across Europe Based on The SHARE Database. *Aging and Disease*, *9*(1), 90–101. https://doi.org/10.14336/AD.2017.0128

National Alzheimer's Coordinating Center (2021). Description of the NACC database. Retrieved from https://www.alz.washington.edu/WEB/data_descript.html

Nguyen, K.-H., Comans, T. A., Green, C., Haapala, I., Biggs, S., & Kurrle, S. (2018). Where are we at with model-based economic evaluations of interventions for dementia? A systematic review and quality assessment. *International Psychogeriatrics*, *30*(11), 1593–1605. https://doi.org/10.1017/S1041610218001291

Prado Lima, M. G., Schimidt, H. L., Garcia, A., Daré, L. R., Carpes, F. P., Izquierdo, I., & Mello-Carpes, P. B. (2018). Environmental enrichment and exercise are better than social enrichment to reduce memory deficits in amyloid-beta neurotoxicity. PNAS Proceedings of the National Academy of Sciences of the United States of America, 115(10), E2403–E2409. https://doi.org/10.1073/pnas.1718435115

Salinas, J., O'Donnell, A., Kojis, D. J., Pase, M. P., DeCarli, C., Rentz, D. M., Berkman, L. F., Beiser, A., & Seshadri, S. (2021). Association of Social Support With Brain Volume and Cognition. JAMA Network Open, *4*(8), e2121122. https://doi.org/10.1001/jamanetworkopen.2021.21122

Seaman, A. T. (2018). The consequence of "doing nothing": Family caregiving for Alzheimer's disease as non-action in the U.S. Social Science & Medicine, 197, 63–70. https://doi.org/10.1016/j.socscimed.2017.12.001

Spreng, R. N., & Bzdok, D. (2021). Loneliness and Neurocognitive Aging. Advances in geriatric medicine and research, 3(2), e210009. https://doi.org/10.20900/agmr20210009

Part 3: Summary

Integration of the Studies

This three-manuscript dissertation was intended to analyze data collected by the National Alzheimer's Coordinating Center [NACC] to identify the level of association between AD diagnosis and exposure to cardiovascular health issues, environmental exposure, and social isolation (NACC, 2021). Although researchers have investigated these issues, the topic has not been explored by selecting a single cohort to identify a level of association between three major risk factors. The specific research problem to be addressed is identifying the level of influence cardiovascular, environmental, and social risk factors have on AD diagnosis. A random selection of (n = 1,229) participants was used for each manuscript. Participants included a varying number of those diagnosed with AD and the presence of elevated amyloid on a PET scan for each manuscript. The results from the data analysis and bivariate logistic regression models provided insight regarding the level of association between the risk of AD and elevated amyloid based on independent variables associated with cardiovascular, environmental, and social risk factors.

Common Themes/Results

Within AD studies, a large body of evidence correlates cardiovascular health issues, environmental exposure, and social isolation as risk factors associated with cognitive decline. The three manuscripts in this dissertation include variables available in the National Alzheimer's Coordinating Center [NACC] Uniform Data Set that align with the literature review. The first manuscript used cardiovascular risk factors associated with

AD known to contribute to the blood-brain barrier's breakdown, impairing the clearance of Aβ found in the brain and the heart (Tini et al., 2020). The second manuscript looks at cigarette smoking and alcohol, which are two of the most prevalent and easily accessible substances associated with AD. Larsson et al. (2017) found that the odds of AD diagnosis correlate with modifiable behaviors, including cigarette smoking and alcohol use. The third manuscript looks at how social interaction, such as a person's living situation (e.g., living with a spouse), level of independence, and type of residence, have varying effects on AD health outcomes. Seaman (2018) explains the negative influences of not receiving care pre and post-AD diagnosis. The author conducted a 26-month ethnographic study of participants with early onset of AD, their families, and healthcare providers.

The common theme found in all three manuscripts is that each model found varying levels of risk associated with cardiovascular health, environmental exposure, and social factors and an AD diagnosis and elevated amyloid-beta plaques on a PET scan. Similar to Tini et al. (2020), the overall model in manuscript one found significance between the combined cardiovascular health variables, including the presence of amyloid-beta plaques and an AD diagnosis. However, there were no significant correlations between individual cardiovascular health variables other than the presence of amyloid-beta plaques. The levels of association measured with an odds ratio indicate positive correlations between poor cardiovascular health and past cardiovascular events.

Modifiable risk factors in the second manuscript were not as similar to what was found in the literature review. Larsson et al. (2017) indicated that AD diagnosis correlates with modifiable behaviors. The overall AD model for modifiable behavior found the

significance of combined modifiable health variables and an AD diagnosis. However, the second overall model for elevated amyloid PET and modifiable health variables was insignificant. Levels of association measured with an odds ratio indicate positive correlations between the current reported use of an anxiolytic, sedative, or hypnotic agent and a negative correlation for years of smoked cigarettes and alcohol abuse regarding elevated amyloid PET and an AD diagnosis.

The third manuscript found significant correlations between social risk factors and an AD diagnosis and the presence of elevated amyloid-beta plaques on a PET scan. Similar to Prodo Lima et al. (2018), the findings in this manuscript indicate that environmental enrichment (EE), such as increased physical activity and social interaction, directly affects a person's risk for developing AD. The AD model found the significance of the combined social isolation variables and an AD diagnosis. Levels of association measured with an odds ratio indicate positive correlations between the reported participant's level of independence regarding elevated amyloid PET and an AD diagnosis.

This dissertation's theoretical framework combines Bronfenbrenner's (1977) Ecological Systems Theory and Finch and Kulminski's (2019) AD Exposome. The Ecological Systems Theory provides a framework that explains the complex system concerning a person's environment and individual development. The approach offers a holistic approach to understanding the nature of a person's environment and potential risk factors for developing Alzheimer's Disease (AD). The three manuscripts support the theoretical framework by statistically modeling levels of variation between risk factors

and elevated amyloid PET and an AD diagnosis. More specifically, cardiovascular health issues, environmental exposure, and social isolation are noted in Finch and Kulminski's (2019) AD Exposome and found to have correlations with elevated amyloid AD diagnosis.

Positive Social Change

Identifying risk factors and promoting early detection/intervention as a protective factor decreases adverse health outcomes associated with AD to encourage increased research and outreach, especially in vulnerable communities, to promote positive social change. The concept of changing behavior to promote healthy longevity impacts individuals and encourages social well-being by lessening the burden of AD on families, communities, and health resources (Nguyen et al., 2018). The potential for AD development and diagnosis increases as individuals live longer, inspiring the need to identify the social determinants of health associated with AD morbidity (Muirhead et al., 2019). A more inclusive understanding of AD risk and modifiable behavioral practices promotes positive social change by altering the disease's progression and decreasing its economic and social burden.

Future Research

There is a need for future studies to examine the effects of cardiovascular health issues, environmental exposure, and social isolation presence of AD and Aβ deposits. Risk factors such as poor cardiovascular health, modifiable behavior, and participants' level of independence regarding elevated amyloid PET and an AD diagnosis were found to be related in this dissertation. Further research is needed to investigate risk factors

found in the literature review, such as modifiable behaviors and social interactions that potentially influence health outcomes

Social demographic variables are also not assessed in this study. Race and ethnicity, educational levels, and economic status should be considered for future studies to identify behavior risk factors within communities, especially those with known inequality and inequity (Lourenco et al., 2018). Including sociodemographic variables in the model could increase the ability of healthcare providers to identify the risk for AD and provide therapeutic interventions before the disease progresses.

Additional recommendations include using other statistical analyses such as linear regression, which uses continuous variables to predict a possible AD outcome. According to Laerd Statistics (2022), a simple linear regression applies two variables to determine an outcome for a dependent variable. Instead of having a complete bivariate model, the linear regression could independently assess the relationship between continuous variables and levels of cognitive decline rather than have yes or no outcomes. The limitation is the lack of information associated with the levels of cognitive decline, which is an additional consideration/recommendation for collecting data that measures the level of cognitive impairment from participants.

Lessons Learned

I used the National Alzheimer's Coordinating Center [NACC] Uniform Data Set for this dissertation, which contains more than 45,000 participants and 166,000 clinical assessments. I selected a random selection of (n=1,229) participants for each manuscript, and participants included a varying number of those diagnosed with AD and the presence

of elevated amyloid on a PET scan for each manuscript. There are numerous variables not included in this study provided by the NACC. I have learned that it is imperative to thoroughly conduct a literature review before selecting independent and dependent variables. The outcomes of following a similar methodology in this dissertation will vary and depend on variable selection.

Conclusion

Alzheimer's disease is a growing epidemic and is the sixth-leading cause of death in the United States. Individuals with AD often have comorbidities due to the aging process, with cardiovascular health hypothesized as correlating with the development of the disease. Participants provided health information collected in the NACC Uniform Data Set (UDS). A random selection of (n = 1,229) participants was selected for each manuscript. Participants included a varying number of those diagnosed with AD and the presence of elevated amyloid on a PET scan for each manuscript. The results from the data analysis and bivariate linear regression models provided insight regarding the level of association between the risk of AD and elevated amyloid based on independent variables associated with cardiovascular, environmental, and social risk factors. I found that factors such as poor cardiovascular health, modifiable behavior, and participants' level of independence regarding elevated amyloid PET and an AD diagnosis were related in this dissertation using bivariate models with multiple variables. However, the majority of independent variables were individually insignificant except for alcohol use and staying at home for elevated amyloid and level of independence for both AD and elevated

amyloid. My findings indicate a knowledge gap regarding AD risk and protective factors, suggesting a need for further research.

Consolidated References

Ali, A.A., Khalil, M.G., Elariny, H.A., Abu-Elfotuh, K. (2017) Study on Social Isolation as a Risk Factor in Development of Alzheimer's Disease in Rats. Brain Disord Ther, *6*(2). https://doi: 10.4172/2168-975X.1000232

Amakiri, N., Kubosumi, A., Tran, J, & Reddy, P. (2019). Amyloid-Beta and MicroRNAs in Alzheimer's Disease. Frontiers in Neuroscience, 13. https://doi.org/10.3389/fnins.2019.00430

Anderson, S. F., Kelley, K., & Maxwell, S. E. (2017). Sample-size planning for more accurate statistical power: A method adjusting sample effect sizes for publication bias and uncertainty. *Psychological Science, 28*(11), 1547–1562. https://doi.org/10.1177/0956797617723724

Bagheri, N., Wangdi, K., Cherbuin, N., & Anstey, K.J. (2018). Combining Geospatial Analysis with Dementia Risk Utilising General Practice Data: A Systematic Review. The Journal of Prevention of Alzheimer's Disease, 5(1):71-77. https://doi.org/10.14283/jpad.2017.33

Bauer, E. A. (2018). The Impact of Frequently Used Antihistamines on Memory in Behaviorally Trained Caenorhabditis elegans.

Bronfenbrenner, U. (1977). Toward an experimental ecology of human development. *American Psychologist, 32*(7), 513-531.

Caldwell, J. Z. K., Berg, J.-L., Cummings, J. L., & Banks, S. J. (2017). Moderating effects of sex on the impact of diagnosis and amyloid positivity on verbal memory

and hippocampal volume. *Alzheimer's Research & Therapy, 9*, 1–10. doi:10.1186/s13195-017-0300-8

Centers for Disease Control and Prevention (2020). Alzheimer's Disease. https://www.cdc.gov/aging/aginginfo/alzheimers.htm

Chen, M., Hu, C., Dong, H., Yan, H., Wu, P., & Alzheimer's Disease Neuroimaging Initiative (2021). A history of cigarette smoking is associated with faster functional decline and reduction of entorhinal cortex volume in mild cognitive impairment. Aging, 13(4), 6205–6213. https://doi.org/10.18632/aging.202646

Chen, Z., Venkat, P., Seyfried, D., Chopp, M., Yan, T., & Chen, J. (2017). Brain–Heart Interaction. *Circulation Research, 121*(4), 451-468. https://doi.org/10.1161/circresaha.117.311170

Dodge, H. H., Goldstein, F. C., Wakim, N. I., Gefen, T., Teylan, M., Chan, K. C. G., Kukull, W. A., Barnes, L. L., Giordani, B., Hughes, T. M., Kramer, J. H., Loewenstein, D. A., Marson, D. C., Mungas, D. M., Mattek, N., Sachs, B. C., Salmon, D. P., Willis-Parker, M., Welsh-Bohmer, K. A., … Weintraub, S. (2020). Differentiating among stages of cognitive impairment in aging: Version 3 of the Uniform Data Set (UDS) neuropsychological test battery and MoCA index scores. Alzheimer's & Dementia (New York, N. Y.), 6(1), e12103. https://doi.org/10.1002/trc2.12103

Drinkwater, E., Davies, C., & Spires-Jones, T. L. (2021). Potential neurobiological links between social isolation and Alzheimer's disease risk. European Journal of Neuroscience, 1– 16. https://doi.org/10.1111/ejn.15373

Durazzo, T. C., Meyerhoff, D. J., & Yoder, K. K. (2018). Cigarette smoking is associated with cortical thinning in anterior frontal regions, insula, and regions showing atrophy in early Alzheimer's Disease. *Drug and Alcohol Dependence*, *192*, 277-284. https://doi.org/10.1016/j.drugalcdep.2018.08.009

Eid, A., Mhatre, I., & Richardson, J. R. (2019). Gene-environment interactions in Alzheimer's disease: A potential path to precision medicine. Pharmacology & Therapeutics, 199, 173-187. https://doi.org/10.1016/j.pharmthera.2019.03.005

Ferrucci, L., & Fabbri, E. (2018). Inflammageing: Chronic Inflammation in Ageing, Cardiovascular Disease, and Frailty. Nat Rev Cardiol, *15*, 505–522. https://doi.org/10.1038/s41569-018-0064-2

Finch, C. E., & Kulminski, A. M. (2019). The Alzheimer's Disease Exposome. *Alzheimer's & dementia: the journal of the Alzheimer's Association*, *15*(9), 1123–1132. https://doi.org/10.1016/j.jalz.2019.06.3914

G*Power 3.1 Manual. (2021). General psychology and industrial psychology. Technical Manual. https://www.psychologie.hhu.de/fileadmin/redaktion/Fakultaeten/Mathematisch-Naturwissenschaftliche_Fakultaet/Psychologie/AAP/gpower/GPowerManual.pdf

Han, L. K. M., Verhoeven, J. E., Tyrka, A. R., Penninx, B. W. J. H., Wolkowitz, O. M., Månsson, K. N. T., Lindqvist, D., Boks, M. P., Révész, D., Mellon, S. H., & Picard, M. (2019). Accelerating research on biological aging and mental health: Current challenges and future directions. Psychoneuroendocrinology, 106, 293–311. https://doi.org/10.1016/j.psyneuen.2019.04.004

Jørgensen, IF, Aguayo-Orozco, A, Lademann, M, Brunak, S. (2020). Age-stratified longitudinal study of Alzheimer's and vascular dementia patients. Alzheimer's Dement, *16*: 908– 917. https://doi.org/10.1002/alz.12091

Kawase, A., Chuma, T., Irie, K., Kazaoka, A., Kakuno, A., Matsuda, N., Shimada, H., & Iwaki, M. (2021). Increased penetration of diphenhydramine in brain via proton-coupled organic cation antiporter in rats with lipopolysaccharide-induced inflammation. Brain, Behavior, & Immunity - Health, 10. https://doi.org/10.1016/j.bbih.2020.100188

Laerd Statistics. (2022). Binomial Logistic Regression. Retrieved from https://statistics.laerd.com/premium/index.php

Langballe, E. M., Ask, H., Holmen, J., Stordal, E., Saltvedt, I., Selbæk, G., Fikseaunet, A., Bergh, S., Nafstad, P., & Tambs, K. (2015). Alcohol consumption and risk of dementia up to 27 years later in a large, population-based sample: the HUNT study, Norway. *European Journal of Epidemiology, 30*(9), 1049-1056. https://doi.org/10.1007/s10654-015-0029-2

Larsson, S. C., Traylor, M., Malik, R., Dichgans, M., Burgess, S., & Markus, H. S. (2017). Modifiable pathways in Alzheimer's disease: Mendelian randomization analysis. BMJ: British Medical Journal, 359.

Lourenco, J., Serrano, A., Santos-Silva, A., Gomes, M., Afonso, C., Freitas, P., Paul, C., & Costa, E. (2018). Cardiovascular Risk Factors are Correlated with Low Cognitive Function among Older Adults Across Europe Based on The SHARE

Database. *Aging and Disease, 9*(1), 90–101. https://doi.org/10.14336/AD.2017.0128

Muirhead, K., Macaden, L., Clarke, C., Smyth, K., Polson, R., & O'Malley, C. (2019). The characteristics of effective technology-enabled dementia education for health and social care practitioners: protocol for a mixed study systematic review. Systematic Reviews, 8(1), 316. https://doi.org/10.1186/s13643-019-1212-4National

National Alzheimer's Coordinating Center (2021). Description of the NACC database. Retrieved from https://www.alz.washington.edu/WEB/data_descript.html

National Institute on Ageing (2017). What is Alzheimer's Disease? https://www.nia.nih.gov/health/what-alzheimers-disease

Nguyen, K.-H., Comans, T. A., Green, C., Haapala, I., Biggs, S., & Kurrle, S. (2018). Where are we at with model-based economic evaluations of interventions for dementia? A systematic review and quality assessment. *International Psychogeriatrics*, *30*(11), 1593–1605. https://doi.org /10.1017/S1041610218001291

Pascoal, T. A., Mathotaarachchi, S., Mohades, S., Benedet, A. L., Chung, C. O., Shin, M., Wang, S., Beaudry, T., Kang, M. S., Soucy, J. P., Labbe, A., Gauthier, S., & Rosa-Neto, P. (2017). Amyloid-β and hyperphosphorylated tau synergy drive metabolic decline in preclinical Alzheimer's disease. *Molecular Psychiatry*, *22*(2), 306-311. https://doi.org/10.1038/mp.2016.37

Peng, B., Yang, Q., B Joshi, R., Liu, Y., Akbar, M., Song, B.-J., Zhou, S., & Wang, X. (2020). Role of Alcohol Drinking in Alzheimer's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis. International Journal of Molecular Sciences, 21(7). https://doi.org/10.3390/ijms21072316

Prado Lima, M. G., Schimidt, H. L., Garcia, A., Daré, L. R., Carpes, F. P., Izquierdo, I., & Mello-Carpes, P. B. (2018). Environmental enrichment and exercise are better than social enrichment to reduce memory deficits in amyloid-beta neurotoxicity. PNAS Proceedings of the National Academy of Sciences of the United States of America, 115(10), E2403–E2409. https://doi.org/10.1073/pnas.1718435115

Salinas, J., O'Donnell, A., Kojis, D. J., Pase, M. P., DeCarli, C., Rentz, D. M., Berkman, L. F., Beiser, A., & Seshadri, S. (2021). Association of Social Support With Brain Volume and Cognition. JAMA Network Open, 4(8), e2121122. https://doi.org/10.1001/jamanetworkopen.2021.21122

Seaman, A. T. (2018). The consequence of "doing nothing": Family caregiving for Alzheimer's disease as non-action in the U.S. Social Science & Medicine, 197, 63–70. https://doi.org/10.1016/j.socscimed.2017.12.001

Simon, S. S. (2021). Good news for dementia prevention: Multiple behavioral features are associated with markers of brain pathology in the preclinical phase of sporadic and autosomal dominant Alzheimer's disease. Biological Psychiatry, 89(8), 739–741. https://doi.org/10.1016/j.biopsych.2021.02.001

Spreng, R. N., & Bzdok, D. (2021). Loneliness and Neurocognitive Aging. Advances in geriatric medicine and research, 3(2), e210009. https://doi.org/10.20900/agmr20210009

Stakos, D., Stamatelopoulos, K., Bampatsias, D., Sachse, M., Zormpas, E., Vlachogiannis, N., Tual-Chalot, S., & Stellos, K. (2020). The Alzheimer's disease Amyloid-Beta hypothesis in cardiovascular aging and disease. *Journal of the American College of Cardiology*, *75*(8), 952-967. https://doi.org/10.1016/j.jacc.2019.12.033

Ricciarelli, R., & Fedele, E. (2017). The Amyloid Cascade Hypothesis in Alzheimer's Disease: It's Time to Change Our Mind. *CURRENT NEUROPHARMACOLOGY*, *15*(6), 926–935. https://doi.org/10.2174/1570159X15666170116143743

Tini, G., Scagliola, R., Monacelli, F., La Malfa, G., Porto, I., Brunelli, C., & Rosa, G. M. (2020). Alzheimer's Disease and Cardiovascular Disease: A Particular Association. Cardiology Research & Practice, 1–10. https://doi.org/10.1155/2020/2617970

Troncone, L., Luciani, M., Coggins, M., Wilker, E. H., Ho, C.-Y., Codispoti, K. E., Frosch, M. P., Kayed, R., & Del Monte, F. (2016). Aβ Amyloid Pathology Affects the Hearts of Patients With Alzheimer's Disease. *Journal of the American College of Cardiology*, *68*(22), 2395-2407. https://doi.org/10.1016/j.jacc.2016.08.073

Tublin, J. M., Adelstein, J. M., Del Monte, F., Combs, C. K., & Wold, L. E. (2019). Getting to the Heart of Alzheimer's Disease. Circulation Research, 124(1), 142-149. https://doi.org/10.1161/circresaha.118.313563

Xue, H., Sun, Q., Liu, L., Zhou, L., Liang, R., He, R., & Yu, H. (2017). Risk factors of transition from mild cognitive impairment to Alzheimer's disease and death: A cohort study. *Comprehensive Psychiatry, 78*, 91-97. https://doi.org/10.1016/j.comppsych.2017.07.003