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Exploring the Association Between Depression and Obesity Among Alzheimer's Patients

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EXPLORING THE ASSOCIATION BETWEEN DEPRESSION AND OBESITY AMONG
ALZHEIMER'S PATIENTS

by

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Bachelor of Science
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Submitted in Partial Fulfillment of the Requirements
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DEDICATION

This document is dedicated to the family and friends that have helped me through this journey. Specifically, I'd like to thank my mother, for always offering her guidance and support throughout my graduate career. Another big thank you goes out to my roommates, who were there for the good times and bad. Thank you all, I truly appreciate it.

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I would like to thank my committee members, for all of their hard work, and willingness to answer my incessant questions. A huge thank you goes to my advisor, Dr. Barr-Anderson, without whom none of this would have been possible. Thank you to Dr. Miller, who made time for me even while taking care of a new baby. Last, but not least, thank you Dr. McLain, whose door was always open for questions.

ABSTRACT

Alzheimer's disease (AD) is a neurological disorder that affects elderly individuals, and is becoming an increasing concern among the aging population of the world. Due to the projected increase in incidence of AD, modifiable risk factors such as depression and obesity should be evaluated, as prevention is the only current option. This study aimed to determine the prevalence of obesity and depression among AD patients, and to evaluate the association between depression and obesity. Patients were chosen from a subset of the South Carolina Alzheimer's disease registry, which included information about weight status and depression, as well as several other comorbidities and other potential confounding variables. All persons in the registry have been diagnosed with AD by a physician. A total of 641 AD patients were included in the study, with 17.6% ($n = 113$) classified as obese, and 53.7% ($n = 338$) self-reporting depressive symptoms. Using several types of regression – linear, logistic, and ordinal logistic – no significant association was found between depression and obesity after controlling for confounding factors (OR of 0.831 [0.545, 1.267], 0.770 [0.489, 1.212] for logistic and ordinal regression, respectively). Linear regression was deemed to be a poor fit for the data, thus could not be used. These null findings could be due to missing potential confounders or relatively small sample sizes. Further study is needed.

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CHAPTER 1

INTRODUCTION

Alzheimer's disease (AD) is a neurological disorder that affects 1 out of every 9 older Americans aged 65 or older (Alzheimer's Association, 2014). It is characterized by amyloid-beta plaques, which are a buildup of the protein amyloid-beta ($A\beta$) on the exterior of neurons, and tau protein tangles on the interior. Symptoms range from dementia, memory loss, changes in mood, confusion, and difficulty completing everyday tasks, to being completely bedridden and dependent on outside help (Alzheimer's Association, 2014; Reitz C, 2014). AD can be diagnosed by a physician after obtaining a family history, and completing a battery of cognitive tests. Magnetic resonance imaging (MRI) may be used to exclude other potential causes of dementia and cognitive impairment, such as stroke. Biomarkers are being researched to more accurately diagnose AD (Shaffer L, 2013; Galluzzi S, 2013; Douaud G, 2013; Roe C, 2013).

As the number one form of dementia in the United States (Hebert L, 2013), AD garners much scientific attention, especially since there is no known cure. Since there is no cure for AD, finding potentially modifiable behaviors and factors becomes very important. Certain non-modifiable factors have been identified as risk-increasing factors. These factors include age (Brookmeyer R, 1997), race (Alzheimer's Association, 2014; Manley J, 2008), family history (Mayeux R, 1991; Rosen A, 2007), and genetic makeup (Breitner J, 1999; Blacker D, 1997; Corbo R, 2007). Among the

modifiable risk factors associated with AD, traumatic brain injury (TBI) (Randolph C, 2013; Guskiewicz K, 2005), hypertension (Glynn R, 1999; Girouard H, 2006), diabetes (Huang C, 2014; Wand K, 2012), and body mass index (BMI) (Whitmer M, 2005; Rosengren A, 2005; Tolppanen A, 2014) stand out as promising areas of focus for prevention. Obesity is perhaps the most easily targeted modifiable risk factor, and can affect several outcomes simultaneously.

Having a BMI greater than 30 kg/m^2 (being obese) is associated with having a higher risk of developing AD. Obesity is also associated with increased risk of diabetes (Whitmer M, 2005; Rosengren A, 2005; Tolppanen A, 2014), and hypertension (Glynn R, 1999; Girouard H, 2006). Therefore, if obesity can be controlled and minimized, so too will several other chronic diseases. This is best done by first understanding what affects obesity. Physical activity level has been found to influence obesity, with the higher the levels of activity, the lower the risk for obesity (Grilo C, 1994).

Socioeconomic status (SES) has also been found to influence obesity (Yaffe K, 2013; Evans D, 1997; McDowell I, 2007), with higher SES levels being associated with a lower risk of obesity.

Depression is yet another risk factor for obesity (Brumpton, 2013; Marmorstein, 2014). The DSM-5 (American Psychiatric Association, 2013) defines depression as depressed mood or loss of interest, as well as several other criteria in a 2 week span.

Being diagnosed with depression has been found to increase the risk of developing AD later in life. The odds of developing AD among those with depression is 1.65 times the odds among those without depression. (Diniz, 2013). While many studies have determined the association between obesity and depression in the general

population, there is a lack of research studying this association among those with AD.

This study aims to fill in this gap, by assessing the association between obesity and depression, among those who have previously been diagnosed with AD. Both obesity and depression are modifiable risk factors, making them ideal candidates for future interventions if they are indeed associated.

CHAPTER 2

LITERATURE REVIEW

Alzheimer's disease

Dementia is defined by the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) as significant irreversible cognitive decline, which requires assistance from another to perform daily activities. Cognitive decline due to dementia cannot be due to delirium, or another neurological disorder. These criteria were originally created in 1984, by the National Institute of Aging, and updated in 2011 (Jack CR, 2011). There are many forms of dementia, many with overlapping symptoms. Criteria were created and updated to enable better diagnosis of major neurological disorders, such as Huntington's disease, dementia due to Lewy bodies, Parkinson's disease, and Alzheimer's disease (AD) (Jack CR 2011; McKhann GM, 2011).

Alzheimer's disease is characterized by amyloid-beta plaques, which are a buildup of the protein amyloid-beta ($A\beta$) on the exterior of neurons. Another hallmark of AD is tangles of hyperphosphorylated tau protein accumulated in the interior of neurons (Alzheimer's Association, 2014; Reitz C, 2014). Symptoms of AD include dementia, memory loss, changes in mood, confusion, and difficulty completing everyday tasks, among others. In the late stages of AD, the patient becomes bedridden and dependent on outside help for even the most basic of tasks. Patients with AD often die from causes other than AD, including cardiovascular and cerebrovascular diseases (Todd S, 2013).

AD is the number one form of dementia in the United States, with an estimated 4.7 million cases in 2010 (Hebert L, 2013). This is also a global issue, with an estimated 24 million cases world-wide (Ferri C, 2005). The prevalence is predicted to increase dramatically over the next 25 to 30 years, (Hebert L, 2013; Ferri C, 2005; Demirovic J, 2003) with an estimated 13.8 million cases in the US, and 81.1 million cases globally.

When diagnosing AD, a physician may utilize magnetic resonance imaging (MRI) to exclude other diseases that may also have dementia-like symptoms, such as stroke (Alzheimer's Association, 2014). Further cognitive testing is performed, along with physical and neurological performance evaluations. A physician will also obtain a medical and family history from the patient, or the patient's medical proxy, if the case is unable to give information themselves. This is to determine if the patient has one or more of the several suspected risk factors for AD. There has been an increased interest on the use of biomarkers and MRI in detecting AD in the early and pre-clinical stages (Shaffer L, 2013; Galluzzi S, 2013; Douaud G, 2013; Roe C, 2013). Recent studies indicate the use of biomarkers increases the accuracy with which physicians can diagnose AD. One such study found misclassification of AD dropped from 41% to 28% when using fluorine 18 fluorodeoxyglucose (Shaffer L, 2013). Another study found when using the AD biomarkers A β 42 and fluorine 18 fluorodeoxyglucose, there was 100% accuracy in diagnosing AD, and 0 patients without the biomarkers developed AD (Galluzzi S, 2013). Other studies found the use of MRI or cerebrospinal fluid biomarkers can allow

physicians to detect cognitive impairment two (Douaud G, 2013) to seven (Roe C, 2013) years before onset of clinical symptoms.

There is no known cure for AD which will stop or reverse the damage done to the neurons by tau tangles and A β plaques. There are several drugs in use currently that help alleviate the symptoms of early- and mid-stage AD (Shah R, 2008; Hansen R, 2008), with cholinesterase inhibitors being the most predominant. These inhibitors are thought to target and decrease the amounts of the precursor of the A β protein, but the mechanism isn't well known (Shah R, 2008). Approaches other than drug mediated therapy are also used in treating the symptoms of AD. Psychosocial interventions – also called nonpharmacological interventions – such as increased social engagement show promise in reducing the severity of AD symptoms (Brodaty H, 2012; Wang, 2002). As with the pharmacological treatments, these interventions only help relieve symptoms. It is of utmost importance to determine risk factors, so AD can potentially be prevented.

Suspected risk factors

Apolipoprotein E Apolipoprotein E (APOE) is a very low density lipid protein that carries cholesterol and cholesterol precursors through the blood stream and to the liver. There are three alleles for the APOE gene: epsilon 2, 3, and 4. The epsilon 3 allele is the most common allele, and thus far isn't believed to play a role in increasing or decreasing the risk of developing late-onset AD (Alzheimer's Disease Education and Referral Center, 2011). In 1994, Corder et al conducted a case-control study that revealed there was a protective association between the less common epsilon 2 and developing late-onset AD (Corder E, 1994). Epsilon 4, on the other hand, has been found to be strongly associated with AD (Breitner J, 1999; Blacker D, 1997; Corbo R, 2007). One

study, the Cache County Study (Breitner J, 1999), found that the maximum age-specific prevalence of AD among those without the epsilon 4 allele was 95. After 95, the prevalence declined. Those with one epsilon 4 allele, the maximum prevalence was at age 87, and in those homozygous for the epsilon 4 allele, the maximum was age 73. Blacker et al (1997) found that heterozygous individuals did not have a statistically lower age of onset as those who have no epsilon 4 alleles. However, compared to those who were homozygous for epsilon 4, the mean age of onset decreased from 72 to 66. This makes APOE-epsilon 4 a tool that may be utilized to predict age of onset among those at risk of AD.

Traumatic Brain Injury Head injuries and their repercussions affect many individuals in a wide variety of lifestyles and occupations. Studies have shown that traumatic brain injury (TBI) is a major concern among those in the military (Weiner M, 2013; Plassman B, 2000), and those in professional contact sports such as boxing and American football (Randolph C, 2013; Guskiewicz K, 2005). TBI is defined as “injury resulting from external force to the head, which results in an alteration or loss of consciousness.” (Weiner M, 2013) Kiraly and Kiraly (2007) estimate the incidence of TBI to be 180/100,000, one of the highest incidences of neurological disorders.

In the past 15 years, TBI – as well as mild TBI – has garnered some attention as a potential risk factor for AD. In 2005, a study found an association between recurrent concussions and mild cognitive impairment among retired football players (Guskiewicz K, 2005). They did not find an association with recurrent concussions and AD, but they saw earlier onset of AD among former players compared to the general population. Plassman et al (2000) used a historical cohort study to estimate the risk of AD among

World War II veterans. There was an increased risk of AD from both moderate and severe head injury, with hazard ratios of 2.32 and 4.51, respectively. Fakhran et al (2013) evaluated the changes in the white matter of the brain after mild TBI, and found the abnormalities were distributed similar to those in the early stages of AD. The exact mechanism of this association is not currently known.

Age Increasing age is the biggest known risk factor for AD (Alzheimer's Association, 2014). As age increases, the risk for developing AD also increases. The majority of people living with AD fall into the 90 years old and above group. In 1997, the proportion of 90+ year olds living with AD was 28.5%, compared to 4.3% of 75 year olds, 8.5% of 80 year olds, and 16% of 85 year olds (Brookmeyer R, 1997). Being elderly doesn't guarantee developing AD, as AD isn't a part of the natural progression of aging.

Family History Having a family history of AD, has been found to be a very significant risk factor for AD. Rosen et al (2007) conducted a case-control study that determined those with AD had an elevated risk of having a family history of AD when compared to those without AD. An earlier study conducted in Manhattan (Mayeux R, 1991) explored the relationship between the risk of dementia and a family history of AD from first degree relatives (parents or siblings). It was noted that there was an increase in the odds of having a first degree relative with dementia in those with AD, as well as those with other types of neurological disorders; thus, an elevated risk for developing a neurological disorder among those with a family history of dementia may not be exclusive to AD.

More recently, studies have shown there is a greater risk among those with a maternal history of AD, compared to no history or only a paternal history (Liu Z, 2013;

Mosconi L, 2007). One such study used cerebrospinal fluid biomarkers A β 1-40 and A β 1-42 to screen cognitively normal individuals (Liu Z, 2013). They found those with a maternal family history of AD had lower A β 1-42 levels than those with a paternal history or no history. This is indicative of potential impaired cognitive function later in life. The authors caution, however, that these results are preliminary, and more research is necessary. Mosconi et al (2007) also found that a maternal family history may increase the risk of developing AD later in life. In this study, positron emission tomography imaging was used to determine the cerebral metabolic rate of glucose (CMRglc) in the brain. Patients with AD tend to have lower rates in specific areas of the brain. They found there was no statistically significant difference between the rates of those with no family history of AD and those with a paternal history of AD. They did find, however, a significant reduction in CMRglc in those with a maternal family history compared to those without a family history.

Gender It was commonly believed that women had a greater risk of developing AD than men. Several studies have since refuted this belief. Kukull et al (2002) found that age stratified incidence rates were similar for men and women, and their 95% confidence intervals overlapped. Hebert et al (2001) also calculated age-specific incidence rates for men and women that were not statistically different. Prevalence also was not significantly different between men and women, even after adjustment for age. It is now known that the appearance of higher risk is due to the fact that women, on average, live longer than men (Hebert L, 2001). The older a person is, the higher the risk of developing AD, regardless of gender.

Race The majority of elderly Americans living with AD are Caucasian (Alzheimer's Association, 2014). This does not mean, however, that white, non-Hispanics are more likely to develop AD. Using self-identified race and a longitudinal study design, Manly et al (2008) found Hispanics and African Americans had higher risks of developing cognitive impairments than whites but African Americans were less likely to report cognitive impairment than whites (Potter et al 2009). Potter et al. also discussed the possibility that other confounding factors are more prevalent in African Americans and Hispanics than whites, such as diabetes and hypertension, which may skew the results of studies (2009).

Diabetes The American Diabetes Association defines diabetes as “a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both” (American Diabetes Association, 2010). Diabetes, especially type 2, has been targeted as a risk factor for AD. Several studies have shown an association between diabetes and AD, yet the mechanism is still unknown. In 2012, a population based cohort study found incidence densities of AD for both men and women with diabetes were higher than those without diabetes, and had a significantly elevated hazard ratio (Huang C, 2014). Another population based cohort study with a longer follow up time (11 years compared to 8) (Wand K, 2012), had similar results: elevated hazard ratios for those with diabetes.

Even with a consensus about the status of diabetes, there are several theories about why diabetes affects the risk of AD, and how. One such theory is diabetes causes increased oxidative stress, which leads to an accumulation of glycation end products (Huang C, 2014). This may lead to abnormalities in the brain, specifically in the

hippocampus. This theory would allow physicians to prescribe pharmaceuticals to combat the negative effects of both diabetes and AD.

Another working theory is that insulin resistance created by diabetes causes brain insulin resistance (Hokama M, 2013; de la Monte, 2014; Craft S, 2004). Increased insulin resistance in the brain may alter the metabolism of the A β protein, the protein responsible for the formation of plaques on the outside of neuron cells. The blood-brain barrier is weakened, and allows insulin to cross into the brain. This may be why diabetics who take insulin have a higher risk of AD than those who do not, as one of the most frequently cited studies discovered (Ott A, 1999). Again, neither of these theories has been proven, but research continues in this area.

Hypertension The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defines hypertension as a blood pressure (BP) reading of higher than 140/90 mmHg (National Institutes of Health, 2010). Pre-hypertension is defined as having a 120-139 mmHg systolic BP or 80-89 mmHg diastolic BP. Those with hypertension are at an increased risk of developing several chronic diseases, AD among the list. Longitudinal data showed the relationship between elevated blood pressure and cognitive decline was U shaped for both systolic (Glynn R, 1999) and diastolic BP (Girouard H, 2006).

Hypertension is a known risk factor for stroke, which damages brain function. This is believed to be due to the brain's need for a continuous, steady supply of blood, which is tightly regulated (Girouard H, 2006). With increased blood pressure, a steady blood supply is interrupted, causing neuron damage and altered gene expression. This, in turn, increases the accumulation of A β and tau proteins in the brain.

Body Weight Body weight is commonly measured as body mass index (BMI), which accounts for an individual's height. Underweight is defined as having a BMI of less than 18.5 kg/m², normal as a BMI between 18.5 and 24.9 kg/m², overweight as a BMI between 25 and 29.9 kg/m², and obese as a BMI of 30 or greater. There has been some debate about whether body weight, specifically mid-life BMI, is a risk factor for AD.

Several studies have been conducted to determine if there is an association between BMI and development of AD, with conflicting results. Several studies have noted there is a J or U shaped association between BMI and AD⁴⁷⁻⁴⁹ (Whitmer M, 2005; Rosengren A, 2005; Tolppanen A, 2014), indicating there is increased risk of AD among those with lower BMI (underweight) and with higher BMI (overweight and obese). On the other hand, other studies have shown there is a protective association between higher BMI and AD (Atti A, 2008; Dahl A, 2008; Luchsinger J, 2013). There is a consensus, however, that a lower BMI, as well as a decrease in BMI in midlife, is associated with a higher risk of AD.

The reason for the differing results of these various studies is not currently known. There may be discrepancies between the different study populations used, or there may be an undefined confounding factor that is causing differing results. There are many factors that affect both risk of obesity/overweight and AD. Several of them will be considered here.

Obesity

As previously mentioned, obesity is defined as having a BMI of greater than 30 kg/m². Further, obesity can be classified into 3 categories: grades 1, 2, and 3. The

corresponding BMI ranges are 30 to <35, 35 to <40, and 40 and above, respectively. In 2011, the overall prevalence of obesity was estimated at 34.9% for adults (Ogden, 2014). The prevalence grade 2 or 3 obesity for men (11.9%) was slightly different than the prevalence for women (17.1%). The prevalence for overweight and obesity among adults is 68.5%. The prevalence is even higher among elderly populations. One population based study found 26.5% of participants were obese, while 39.9% were classified as overweight (Ricci, 2014). Ogden et al found the national prevalence of obesity for those age 60 years and older was slightly higher than that of all adults: 35.4% (2014).

The high prevalence of obesity and overweight is bound to take a toll on the population, both in terms of morbidities and monetary costs. The effect of obesity on overall health is akin to an increase in age by 30 years (Strum R, 2002). This is similar to the effects of smoking, or heavy drinking. Obesity increases the risk of developing cardiovascular disease, hypertension, and diabetes more-so than drinking or smoking. These chronic diseases are fairly common, and persist for a long period of time, which increases the cost burden. It has been estimated that obesity is responsible for a 36% increase in health care costs, and a 77% increase in medications costs (Strum R, 2002).

There are several factors known to increase the risk of developing obesity. For an adult, these factors include but are not limited to smoking, amount of physical activity, and nutrition (Lakhan S, 2013). Depression, hypertension, and diabetes are also risk factors for AD.

AD risk factors related to obesity

As mentioned previously, hypertension is a risk factor for AD, but it is also known to be associated with obesity as well. Obesity has been shown to be associated

with hypertension (Lee S, 2005; Mokdad A, 2003), but the association is likely confounded by several other factors. These include nutrition, age, race, and other chronic diseases. In general, a higher BMI is associated with a higher risk of hypertension.

Much like hypertension, diabetes is also related to both AD and obesity. Diabetes has garnered much attention from the scientific world due to its high prevalence (about 285 million adults worldwide [Shaw J, 2010]), and the predictions that it will continue to increase in the next 20-30 years. Studies have noted that an elevated BMI increases the risk of developing diabetes (Mokdad A, 2003). This is also likely to be confounded by several other factors, many of which are also shared by hypertension. These include physical activity, obesity, age, and nutritional factors.

Factors affecting AD and obesity

Physical activity There is a vast amount of literature on the association between physical activity and obesity. An increased amount of physical activity is associated with a lower risk of obesity (Grilo C, 1994). This inverse relationship has been studied extensively over the past 10 to 15 years. A similar protective association has been seen between physical activity and AD. Cohort data have shown that higher levels of physical activity are associated with lower risk of AD, as well as cognitive impairment (Laurin D, 2001).

It is unknown whether this association is due to an effect physical activity has on the body, and specifically on the brain, or if it has to do with the lower risk of obesity. As previously discussed, obesity is believed to be a risk factor for AD. With a higher amount of physical activity, there would be a lower risk of obesity, and by proxy, a lower risk of developing AD.

Socioeconomic Status The American Psychological Association defines socioeconomic status (SES) as “the social standing or class of an individual or group, (2014)” which can be measured in several ways. Commonly, annual household income, education level, or occupation is used as an indicator for SES. A combination of several factors may also be used, in a type of metric to more accurately determine SES. In general, lower household income, education level, and property value is indicative of a lower SES.

SES has been found to be associated with a number of chronic diseases, obesity and AD among them. When using level of education as an indicator for SES, the lowest level showed a strong association with AD when compared to the highest SES level. Several studies showed the estimated risk nearly doubling (Yaffe K, 2013; Evans D, 1997; McDowell I, 2007) with the lowest level of education. There is some concern that using education levels as a surrogate for SES may bias the estimate. Most studies use cognitive exams such as the Modified Mini-Mental State exam to screen for subjects with cognitive decline. Unfortunately, these exams tend to be correlated with education level, which means exams shouldn't be used when exploring the association between cognitive decline and education level. This can be remedied by using a different indicator of SES.

Another way researchers can estimate SES is by using occupational hierarchy. Unskilled laborers are considered lower SES than those in management positions. When using occupation, there was still an association between SES and AD, albeit to a lesser extent (Evans D, 1997; McDowell I, 2007). Using annual household income generally gave the same results as education level (Yaffe K, 2013; Evans D, 1997; McDowell I, 2007), and is probably one of the most accurate measures of SES available.

SES is similarly associated with obesity. When using education level or income, there is a strong association between the lowest SES levels and AD when compared to the highest SES levels (Conklin A, 2013; Drewowski A, 2014). When using self-reported financial hardships – another surrogate for SES – the association between the lowest category and AD was still significant, but not as strong (Conklin A, 2013). While these associations generally hold true in most populations, it is not true for all (Mowafi M, 2014). Most likely, there are other factors confounding this association, such as food availability.

Depression The DSM-5 (American Psychiatric Association, 2013) defines depression as depressed mood or loss of interest, as well as 4 or more other criteria in a 2 week span. The other potential criteria that may indicate depression are: weight loss or gain, insomnia, fatigue, retardation, feelings of worthlessness, inability to concentrate, and thoughts of suicide. This is normally diagnosed using one of several depression scales available. With therapy and proper pharmaceutical use, depression can be treated and managed successfully.

Prospective cohort data have shown an association between obesity and depression (Brumpton B, 2013; Marmorstein N, 2014). There is some discrepancy as to whether the prevalence of depression is different by gender. However, the consensus is, regardless of gender, adults with depression have a higher risk of being obese than those without depression. The HUNT Study (Brumpton B, 2013) found having anxiety or depression was associated with an increase in weight, and an increased cumulative incidence in obesity.

Depression has also been investigated for its association with AD. Longitudinal data analyzed with proportional hazard regression found a slight association between depression and AD incidence (Luppa M, 2013). Another longitudinal study looked for an association between AD and present depression, past depression, and both present and past depression (Olazaran J, 2013). A weak association was found between AD and present depression, and a stronger association between AD and past and present depression. The inclusion of past depression distinguishes between a true association and potential reverse causation. Depression is also a symptom of AD, which makes finding an association between depression and AD more difficult.

According to Lyketsos et al. 27% of AD patients suffer from mild depression, and 21% suffer from major depression (1997). A meta-analysis performed by Diniz et al. showed a significant increase in the risk of developing AD among those with depression (2013). Analyzing 23 community-based prospective cohort studies, Diniz et al. found late-life depression, specifically, was associated with increased risk of all-cause dementia, as well as AD and vascular dementia. According to their analysis, there was a significant odds ratio of 1.65 (95% CI 1.42 – 1.92) for the association between late-life depression and AD.

The exact mechanism of this association isn't known, but a common hypothesis is that depression causes degradation of neurons. This eventually accumulates, and leaves the brain more susceptible to dementia (Olazaran J, 2013). Another hypothesis is there are specific gene polymorphisms that cause depressive symptoms, and increases the risk of developing AD. One study focused on the Sirtuin 2 gene, the function of which is as of yet unknown (Porcelli S, 2013). Specifically, Porcelli et al. focused on the rs10410544

polymorphism, which has been implicated in several different mental illnesses, including depression. Upon further analysis, Porcelli et al. discovered no association between the rs10410544 polymorphism and AD. However, there are still many others that need to be investigated for potential links.

It has already been established that AD and obesity are associated, as well as AD and depression. While there have been several studies assessing the association between obesity and depression, there is a lack of information on this association among those who have been diagnosed with Alzheimer's disease. This study aims to fill this void, to determine if there is in fact an association between obesity and depression among those with AD. The results of this study could identify which areas of prevention should be focused on to alleviate symptoms of AD, as well as possible prevention of AD itself.

CHAPTER 3

METHODS

Research question This study aimed to determine whether there was an association between depression and obesity (having a BMI greater than 30kg/m^2) among a population of adults who have been diagnosed with AD.

Hypotheses

1. The prevalence of depression in this population is around 50%, approximately the percentage of mild and major depression in AD patients found by Lyketsos et al (1997).
2. The prevalence of obesity in this population (mean age= 83 ± 8.18 years) is higher than the national prevalence of obesity for older adults: 35.4%.
3. There is a positive association between depression and obesity; those AD patients who are depressed are more likely to be obese, compared to those who are not depressed.

Study population The South Carolina Alzheimer's Disease Registry is a statewide population-based registry for those who are diagnosed with AD, as well as other related disorders. These include vascular dementia, Parkinson's disease, dementia with Lewy

Bodies, and dementia due to stroke, among others. Data on diagnosed cases were obtained from several sources, including inpatient hospitalizations, Medicaid, mental health records, vital records, and long-term care facilities in the state of South Carolina.

A participant's type of dementia was classified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes provided from the physician's diagnosis. In this registry, AD was classified by the ICD-9-CM codes 290.0-290.3, 290.8-290.9, and 331.0. Along with diagnosis, information about sociodemographic variables and other medical diagnoses were obtained at the time of entry into the registry. A total of 82,772 participants are included in the registry. Of those, 50,961 participants have been diagnosed with AD. The current study used a smaller subsample of the registry, the Eli Lilly subsample, which included more detailed information related to depression scores and general health scores. The surveys were answered by caregivers, not the patients themselves. In this way, information was collected about appetite disturbances, depressive symptoms, and several comorbidities. These comorbidities include, but are not limited to: hypertension, myocardial infarction, congestive heart failure, Peripheral Vascular Disease, Cerebral Vascular Disease, dementia, chronic obstructive pulmonary disease (COPD), diabetes, moderate/severe renal disease, any tumor, and acquired immune deficiency syndrome (AIDS). In total, 641 persons with AD were analyzed for this study, the majority of whom had complete data. While this greatly reduces the number of participants, the subset contains much more detailed and pertinent information about depression, the main independent variable for this study.

Variables

Depression Depression was defined two ways: as a dichotomous variable and a continuous score. For the dichotomous variable, caregivers were asked if the patient seemed sad or depressed, or if the patient states they are sad/depressed. Response options were yes and no. There were also several other questions related to depression and sadness, which can be seen in Appendix A.1. To prevent redundancy, only the umbrella, yes/no variable was analyzed. The continuous depression variable was calculated by multiplying the responses to depression frequency and depression severity. Thus the higher the depression score, the more severe the case of depression. The questions used to ascertain the depression score can be seen in Appendix A.1. The dichotomous variable was used in logistic regression models, while the continuous variable was used in the linear regression models. The continuous and dichotomous variables were not used in the same models together, to prevent redundancy.

Weight status Using the height and weight measurements collected by nurses during the data collection for the AD registry, a continuous BMI variable was calculated (weight in kilograms/ height in meters squared).

Obesity status Obesity is based on patients' BMI. A BMI of less than 18.5 kg/m² is classified as underweight; BMI between 18.5 and 24.9 kg/m² is classified as normal weight, BMI between 25 and 29.9 kg/m² is classified as overweight, and BMI of 30 kg/m² or greater is classified as obese. For logistic regression models, a dichotomous (yes/no) obesity status variable was created using BMI cut-off point of 25 kg/m².

Appetite disturbances Appetite disturbance was defined two ways: as a dichotomous variable and a continuous score. For the dichotomous variable, caregivers were asked if the patient has had any change in appetite, weight, or eating habits, or if there had been any changes in the type of food the patients preferred. Response options were yes and no. There were also several other questions related to appetite disturbances, which can be seen in Appendix A.2. To prevent redundancy, only the umbrella, yes/no variable was analyzed. The continuous appetite disturbance variable was calculated by multiplying the responses to appetite disturbance frequency and severity. Thus the higher the appetite disturbance score, the more severe disturbance. The questions used to ascertain the appetite disturbance score can be seen in Appendix A.2.

Age The numerical variable age was calculated from the date of birth, on the day of the interview.

Gender The gender variable is categorical; patients were categorized as male, female, or unknown.

Comorbidities A modified Charlson Comorbidity Index (CCI) was used to assess overall health of the AD patient. The CCI variable was a continuous variable, with the higher the score, the more comorbidities an individual has, thus the poorer the patient's overall health. The comorbidities included in this CCI were: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, dementia, COPD, diabetes, moderate/severe renal disease, presence of any tumor, and AIDS. Based on previous literature, only these specific comorbidities were chosen to be included in the CCI for this study.

The above mentioned covariates were investigated for confounding and effect modification. These were chosen for investigation based on previously published literature.

Statistical Analysis All statistical analysis was done using SAS 9.3 (Cary, NC). The association between depression and weight status was determined using several different methods. This was done to determine several possible relationships. Linear regression was used to determine if there was a linear relationship between the continuous BMI variable and continuous depression score variable. Logistic regression was used to determine an association between the dichotomous weight status variable (obesity yes/no) and depression, and multinomial regression was used to determine the association between a categorical weight status variable (underweight, normal, overweight, and obese) and depression. For each type of regression, several independent variables were evaluated for inclusion in the model. Age, CCI, race, sex, specific comorbidities (diabetes, hypertension, and heart disease), appetite disturbances (dichotomous or continuous), and home ownership were the covariates investigated in each model.

Using univariate logistical regression, a crude association between depression and obesity was assessed, using a dichotomous outcome, and a dichotomous exposure. Covariates were added to the regression model one at a time, and assessed for statistical significance. This method was applied to all regression models used in this study. Statistical significance was set at $\alpha=.05$. Once a significant covariate is added to the model, all previous insignificant covariates were added back into the model to check for significance in the new model. These covariates included gender, race, age, and other medical conditions. Individual medical conditions were considered (including diabetes,

hypertension, and cancer), determined by a yes/no response to several questions about comorbidities, as well as the CCI calculated from the previously listed comorbidities. Once the full multivariate logistical regression model was established, the association between depression and obesity was assessed.

To determine if there is a linear relationship between depression and weight status, a simple linear regression model was run using continuous BMI variable and continuous depression score in SAS. Then, using the method described above, a final model was created. To determine if the data follow a linear trend, the adjusted R square values were recorded. To check for non-linear trends, the continuous BMI variable was transformed in several ways: squared, cubed, and standardized. The adjusted R square values were recorded for these regression models as well.

Finally, a multinomial regression analysis was performed, to reinforce the findings from the previous logistic analysis. Using the same variables as the previous analysis, a full model was assembled. The outcome variable used was BMI classified into 4 groups: underweight, normal weight, overweight, and obese according to the ranges indicated previously. Ordinal logistic regression was used to obtain an odds ratio and confidence interval.

A -2 log likelihood ratio test was performed to determine if the full model was necessary to obtain the most accurate estimate, or if the crude model was sufficient.

CHAPTER 4

RESULTS

Study population The caregivers of 641 AD patients responded to the Eli Lilly survey. Of those that responded, the Alzheimer's patients they care for were predominantly female (75%). The mean age of the population was 83 ± 8.37 years old (range from 53 to 101 years of age at the time of the interview). A total of 113 patients (17.6%) were classified as obese, while 528 were either underweight (n=86), normal (n=288) or overweight (n=154). A high percentage of patients were diagnosed with hypertension in both the obese and non-obese groups (86.7% and 73.5%, respectively). A significantly higher proportion of obese patients indicated they had been diagnosed with diabetes, compared to the non-obese patients (p=0.001). Those in the obese category had a significantly lower mean age compared to those in the non-obese category (81 years and 84 years, respectively; p-value: 0.0011). Table 1 contains the demographic information on this population

Table 4.1. Demographic information of adults with Alzheimer's disease

	Obese (n=113)	Non-obese (n=528)	p-value
Sex, n(%)			0.4171
Male	20 (22)	105 (26)	
Female	72 (78)	302 (74)	
Age, mean(SD)	81.42 (8.37)	84.18 (8.01)	0.0011
Depression, n(%)	57 (50)	281 (53)	0.8537
	Obese (n=113)	Non-obese (n=528)	p-value

Depression Score, mean(<i>SD</i>)*	2.35 (3.39)	2.63 (3.55)	0.4851
Appetite disturbances, n(%)	49 (43)	226 (43)	0.9750
Appetite disturbance score, mean(<i>SD</i>)**	2.52 (3.63)	2.59 (3.72)	0.8486
Race, n(%)			0.3415
White	52 (46)	269 (51)	
Other	61 (54)	259 (49)	
Charlson Comorbidity Index, mean(<i>SD</i>)	5.86 (1.88)	5.88 (1.78)	0.9292
Heart Disease, n(%)	22 (19)	105 (20)	0.9195
Hypertension, n(%)	98 (87)	388 (73)	0.0029
Diabetes, n(%)	50 (44)	150 (28)	0.0010

*Defined as depression frequency multiplied by depression severity. Score ranges from 0 to 12.

** Defined as appetite disturbance frequency multiplied by appetite disturbance severity. Score ranges from 0 to 12.

Prevalence The prevalence of obesity in this study, as stated earlier, was 17.6% (CI: [14.8% , 20.8%]), while the prevalence of overweight adults in this study population (n=154) was 24% (CI: [20.8% , 27.5%]). A total of 338 patients had self-reported depression, a prevalence of 53.7% (CI: [49.8% , 57.7%]). Twelve caregivers declined to respond to the depression section of the survey.

Association between depression and obesity The main outcome modeled in this study was obesity. Using logistic regression, a crude association between depression and obesity of 0.89 was obtained, however it was insignificant (CI [0.591, 1.342]). An adjusted odds ratio was obtained using model 4, which can be seen in table 4.2 in greater detail. Several variables were considered for the full model, including: sex, Charlson Comorbidity

Index, race, and appetite disturbances. All of these, however, were insignificant in a model with depression only ($\alpha = 0.05$).

Table 4.2. Model descriptions and β values for logistic regression

	Model 1	Model 2	Model 3	Model 4
Depression	-0.1162	-0.1560	-0.1827	-0.1855
Age		-0.0397*	-0.0419*	-0.0379*
Hypertension			0.8803*	0.7756*
Diabetes				0.5042*
Odds Ratio [95%CI]	0.890 [0.591, 1.342]	0.856 [0.564, 1.298]	0.833 [0.547, 1.268]	0.831 [0.545, 1.267]

* indicates significant p-value

Once the model was created, a protective adjusted odds ratio of 0.83 was obtained. This was, like the crude estimate, not statistically significant (CI [0.545, 1.267]). While neither the original crude model (model 1) nor the final adjusted model (model 4) produced a significant estimate, a -2 Log Likelihood determined the full model was a better fit than the original model (data not shown).

To ensure the results obtained above weren't due to the classification of patients used in logistic regression, ordinal logistic regression was used to obtain another measure of association, using a four group classification (underweight, normal, overweight, and obese). A crude association of .99 was found, but like the estimate obtained previously, it was insignificant (CI [0.75, 1.33]). Using the previously described method, a model including several covariates was created. The final full model (model 5) can be seen in detail in table 4.2.

Table 4.3. Model descriptions and β values for ordinal logistic regression

	Crude Model	Full Model
Depression	-0.2171	-0.2617
Age		-0.0340*
Hypertension		0.7821*

	Crude Model	Full Model
Diabetes		0.5125*
Appetite Score		0.00272*
Odds Ratio [95% CI]	0.805 [0.518, 1.250]	0.770 [0.489, 1.212]

* Indicates significant p-value

Table 4.4. Comparison of weight statuses using ordinal logistic regression

	Odds ratio [95% Confidence Interval]
Underweight	<0.001[0.392, 1.100]
Overweight	0.913 [0.609, 1.368]
Obese	0.770 [0.489, 1.212]

Like the previous logistic regression results, all odds ratios were insignificant. Also like the estimates from logistic regression, the crude and adjusted odds ratios were below 1. The adjusted odds ratio obtained from the full model showed reduced odds of having depression among those who are classified as obese, compared to those who are classified as normal weight, when other variables are held constant. When comparing the overweight population to the normal weight group, the odds increased to nearly 1 (0.913 [0.609, 1.368]), as seen in Table 4.4. As seen in the other regression analyses, none of the odds ratios obtained were significant.

Linear regression was used to analyze a potential linear trend between the continuous BMI variable and depression. It was determined there was not a linear trend, as the adjusted r^2 for both the crude association and the adjusted model was very small (0.002 and 0.0584, respectively) when the generalized linear model (GLM) procedure in SAS was used. The continuous BMI variable was transformed in several ways, to assess for a non-linear trend. The first transformation assessed was BMI^2 , the adjusted r^2 dropped to 0.0165 for the adjusted model. For BMI^3 , the adjusted r^2 for the adjusted

model dropped even further to 0.0082, much lower than the non-transformed variable. Finally, the BMI variable was standardized, which increased the adjusted r^2 to 0.0224, which was still lower than the un-transformed variable.

CHAPTER 5

DISCUSSION

The prevalence of obesity among the population of AD patients was 17.6%, which is less than the national prevalence of older adults of 35.4%, as determined by Ogden et al (2014). A test of proportions showed the prevalence obtained in this study was significantly different than the prevalence obtained by Ogden et al. (Z test statistic: -8.58; p-value: <0.0001). The same was determined for overweight; the prevalence of overweight adults was 24.0%, lower than the national prevalence of 33.6% (Ogden et al, 2014). These findings, which are contrary to our hypothesis, may be due in part to the small number of participants. The fact that the average age of the population was in the mid-80s may also contribute to the lower percentage of overweight and obese individuals. A recent study conducted on modifiable risk factors of AD reported the prevalence of obesity among AD patients to be 28% (Chen, 2014). This was also lower than the national prevalence, but was higher than the prevalence of this study. The older population Chen et al. studied had a mean age of 70 years, still much lower than this study.

One potential explanation for the lower than expected obesity and overweight prevalence is due to the age and nature of the population in this study. The population had a high mean age, and all participants were diagnosed with AD. This indicates that most of the participants were in the later stages of AD, which is characterized by loss of

appetite and trouble swallowing (Alzheimer's Association, 2014). This leads to weight loss and frailty. This frailty could be the reason such a low prevalence of obesity was seen. On the other hand, the overall prevalence of depression among this study population was 53.7%, higher than the 48% Lyketsos et al found in 1997. This aligns with the hypothesis that the prevalence of depression in this study would be around 50%, similar to the previously mentioned study. A test of proportions showed the prevalence obtained in this study was not significantly different than the prevalence obtained by Lyketsos (Z test statistic: 2.89; p-value: .9981). Although the Lyketsos study is nearly 20 years old, the trend remains that there is a high proportion of AD patients that experience depression (Lyketsos, 1997).

While not statistically significant, there was a protective association between depression and obesity found in this study. This is the exact opposite of what was hypothesized, and what had been previously published. Brumpton et al. found both men and women who had depressive symptoms had an increased risk of being obese (relative risks of 1.37 and 1.18, respectively) (2013). However, Brumpton et al. did not look at those specifically with AD, thus a direct comparison cannot be made. Likewise, Brook et al. found women with psychological issues such as depression were more likely to report less physical activity, which was directly associated to higher BMI (2013). While many of these studies dealt primarily with adolescents, Pan et al. found depression to be associated with obesity (odds ratio of 1.38) among middle aged and elderly women without AD (2012). The difference in findings from previously published literature may be due to there being very little difference between the proportions of AD patients with depression among the obese/non-obese groups (See Table 4.1). The obesity groups were

broken down further, to determine if this was causing the insignificant protective association. Regardless of how the patients were grouped (2, 3, or 4 categories), there remained no significant differences in the proportions of depressed individuals. The odds ratio increased to 1.23 when multinomial regression was used, but remained insignificant.

While the results of this study were not as expected, there is a potential explanation for the protective association found. As previously mentioned, this study population had a relatively old mean age, indicating the patients more than likely were farther along in the progression of AD. Late stage AD is characterized by both depression (the main exposure of interest) and increased frailty. This could cause the association to be skewed toward a protective association.

A linear model to evaluate the association between continuous BMI and depression was determined to be ineffective. There is not a strict linear relationship between continuous BMI and continuous depression score. Based on the adjusted r-squares calculated, a linear model fits the data very poorly, thus linear regression was rejected as reasonable method for estimating the association between depression and obesity. This held true even after a set of different transformations were applied to the BMI variable. All transformations resulted in a poorer fit for the adjusted models than the untransformed BMI variable.

This study has several strengths. This study focused on a very specific population, one that is of the utmost importance, as the prevalence of AD is expected to dramatically increase in the next few decades. While several studies have focused on the relationship

between depression and obesity, it has not really been studied among AD patients. Thus, this study attempts to fill in that gap.

The use of multiple types of analyses to determine the true odds of depression is also considered a strength. While a linear analysis was ruled ineffective, both the logistic and multinomial regression analyses concluded there was no significant relationship between depression and obesity. Using multiple types of regression reinforced the results obtained, indicating the estimates calculated are more than likely correct. This means there most likely is not a true significant relationship between depression and obesity among AD patients in this population.

This study also has a few limitations. The overall number of patients classified as obese was relatively low, as was the total number of participants, compared to the number of AD patients in the registry. Hence, the power of this study may be lowered.

Perhaps the biggest limitation to this study was the method of collecting certain information. While information such as age, height, weight, and comorbidities were collected by nurses directly from the AD patients, information on depression and appetite disturbances was obtained from caregivers of the patients. This leads to potential misinformation, and also has the potential to introduce recall bias.

Another limitation to this study was a lack of certain confounders being ascertained in the dataset. Other than home ownership (which was found to be insignificant in all analyses), there were no socioeconomic variables available to include in the analysis. SES has been found to be a significant variable when analyzing associations between both AD and depression (Yaffe K, 2013; Evans D, 1997; McDowell

I, 2007), and there was no way to control for it in this study. There were also no measures of APOE taken in this study – another variable that should be controlled for during analyses. Since APOE may be associated with an increased risk of depression, it may be a potential confounder (Breitner J, 1999; Blacker D, 1997; Corbo R, 2007). Not having these two key pieces of information is seen as a limitation, as it may be masking the true association between depression and obesity among this group of AD patients. With the addition of these two variables, the protective association found using logistic regression may have been closer to the null value of 1.

CHAPTER 6

CONCLUSIONS

This study determined there was no significant association between depression and obesity among adults diagnosed with AD. This was opposite of what was expected, and what had been reported in previous studies. This may be due to the previously mentioned limitations, or some other as of yet unknown circumstances.

Due to the drastic increase in expected number of AD patients in the future (Reitz, 2014), it is imperative that modifiable factors that affect the risk of developing AD are well understood. As there is currently no cure for AD, prevention is the only option for decreasing the incidence. This study did not find evidence of an association between depression and obesity; however, based on the limitations mentioned previously, the steps described below need to be taken to completely rule out an association.

A potential future study should include SES information, as well as information about APOE in the AD patients. A study with a larger population of adults with AD, and clinically diagnosed depression instead of caregivers' opinions would be ideal in either refuting or confirming the results of this study. Potentially, the study could be repeated, using patients from the full AD registry, and obtaining the missing information directly from the AD patients themselves, or the caretakers who would be able to provide the desired information.

There is still a knowledge gap in the literature surrounding the associations between several risk factors among AD patients. This study attempted to fill that gap for obesity and depression, however, based on the findings, the results should be cautiously interpreted. As mentioned previously, further study is needed in this area, as well as other potential modifiable risk factors.

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APPENDIX A – QUESTIONS USED FOR DEPRESSION VARIABLES

Table A.1 Survey questions used for depression variables

Variable	Question	Response choices
Depression (Categorical)	Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed?	Yes/No
	Does the patient have periods of tearfulness or sobbing that seem to indicate sadness?	Yes/No
	Does the patient say, or act as if, he/she is sad or in low spirits?	Yes/No
	Does the patient put him/herself down or say that he/she feels like a failure?	Yes/No
	Does the patient say that he/she is a bad person or deserves to be punished?	Yes/No
	Does the patient seem very discouraged or say that he/she has no future?	Yes/No
	Does the patient say he/she is a burden to the family or that the family would be better off without him/her?	Yes/No
	Does the patient express a wish for death or talk about killing himself/herself?	Yes/No
	Does the patient show any other signs of depression or sadness?	Yes/No

Variable	Question	Response Choices
Depression Frequency	Frequency?	Rarely - less than once per week Sometimes - about once per week Often - several times per week but less than every day Very often - essentially continuously present
Depression Severity	Severity?	Mild - depression is distressing but usually responds to redirection or reassurance. Moderate - depression is distressing; depressive symptoms are spontaneously voiced by the patient and difficult to alleviate. Severe - depression is very distressing and a major source of suffering for the patient.

APPENDIX B – QUESTIONS TO CREATE APPETITE DISTURBANCE VARIABLES

Table B.1 Survey questions to create appetite disturbance variables

Variable	Question	Response Choices
Appetite (Categorical)	Has he/she had any change in appetite, weight, or eating habits (count as NA if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?	Yes/No
	Has he/she had a loss of appetite?	Yes/No
	Has he/she had an increase of appetite?	Yes/No
Appetite (Categorical)	Has he/she had a loss of weight?	Yes/No
	Has he/she had an increase of weight?	Yes/No
	Has he/she had a change in eating behavior such as putting too much food in his/her mouth at once?	Yes/No
	Has he/she had a change in the kind of food he/she likes such as eating too many sweets or other specific types of food?	Yes/No
	Has he/she developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order?	Yes/No
	Have there been any other changes in appetite or eating that I haven't asked about?	Yes/No
Appetite disturbance frequency	Frequency	Rarely - less than once per week Sometimes - about once per week Often - several times per week but less than every day Very often - once or more per day or continuously

Variable	Question	Response Choices
Appetite disturbance severity	Severity	<p>Mild - changes in appetite or eating are present but have not led to changes in weight and are not disturbing</p> <p>Moderate - changes in appetite or eating are present and cause minor fluctuations in weight</p> <p>Severe - obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing, or otherwise disturb the patient</p>