BODY MASS INDEX AS A PREDICTOR FOR MILD COGNITIVE IMPAIRMENT

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DEDICATION

I dedicate this thesis to my late grandmother, Katherine Navarrete, who struggled nearly a decade with Alzheimer’s disease, and to my mother, Toni De Vera, who cared for her during this difficult time. Everything I do and everything I am is rooted in the both of you. This is for you.
ABSTRACT OF THE THESIS

Body Mass Index as a Predictor for Mild Cognitive Impairment
by
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Mild cognitive impairment (MCI) is a condition characterized by cognitive decline that is not part of the normal aging process yet does not constitute dementia. Studies suggest that MCI risk increases with age, however there is less certainty regarding modifiable risk factors, such as body mass index (BMI). The purpose of this study was to primarily examine the association between incident MCI and BMI, with a secondary interest in the effect of ethnicity. This survival analysis drew data from the University of California, San Diego (UCSD) Shiley-Marcos Alzheimer’s Disease Research Center (ADRC) Longitudinal Study. Cox proportional hazards regression was used to investigate the relationship between incident MCI and BMI, in addition to its association with ethnicity, age, apolipoprotein E ε4 (APOE ε4) allele presence, sex, family history of dementia, history of diabetes, Dementia Rating Scale (DRS) score, and Mini-Mental Status Exam (MMSE) score. Of the 339 Normal Controls enrolled in the ADRC Longitudinal Study and met analysis criteria, 59 (17%) developed MCI within the study period. Among participants, 137 (40.4%) were considered underweight or normal, 131 (38.6%) were considered overweight, and 71 (20.9%) were considered obese. In the bivariate and multivariable analyses, BMI was not found to be significantly associated with incident MCI prior to adding a BMI x ethnicity interaction term. Age and APOE ε4 presence, however, were significantly associated with the outcome individually (p<0.005 and p<0.05, respectively) and after controlling for other covariates in the final model (p<0.001 and p<0.005, respectively). Additionally, the interaction between BMI and ethnicity was significantly associated with MCI risk. Among non-Hispanics, those who were obese were 2.34 times more likely to develop MCI compared to those who fell into the normal or underweight BMI category (p=0.0127, 95% CI 1.06-5.17), after adjusting for age and APOE ε4 presence. However, an opposite effect was determined in Hispanics. Among Hispanics, those who fell within the underweight or normal BMI category were 3.57 times more likely to develop MCI compared to those who were obese (p=0.0127, 95% CI 0.81-14.29). Further investigation into this BMI-ethnicity relationship is needed to better understand how BMI affects MCI risk.
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CHAPTER 1

INTRODUCTION

BACKGROUND

Mild cognitive impairment (MCI) is a condition characterized by mild changes in thinking abilities that are noticeable to the affected individual and to family and friends without affecting an individual’s ability to execute activities of daily living (ADLs) or instrumental activities of daily living (IADLs; Thies & Bleiler, 2013). The cognitive decline associated with MCI does not constitute dementia, yet it is not part of the normal aging process (Gauthier et al., 2006; Petersen, 2004). Studies have estimated that approximately 10-20% of individuals age 65 and older have MCI (Thies & Bleiler, 2013). This suggests that anywhere from 4.5 million to 8.9 million adults age 65 years and older are living with MCI in the United States (U.S.) alone (Thies & Bleiler, 2013; United States Census Bureau, 2014). In addition, an average MCI incidence rate of 12 to 15 per 1000 person-years for individuals 65 years and older has been estimated (Bischkopf, Busse, & Angermeyer, 2002). Studies suggest that the risk of MCI increases with age and may also be associated with ethnicity, gender, level of education, and history of cerebrovascular disease, among other factors (Cherbuin et al., 2009; Kivipelto et al., 2001; Lopez et al., 2003).

Recently, MCI has gained an increasing interest within the field of aging and dementia. Specifically, researchers are focusing efforts on identifying an early stage of Alzheimer’s disease (AD). AD is the most common form of dementia, and in 2013 an estimated 5.2 million Americans had AD (Alzheimer's Association, 2014a). This number is expected to increase dramatically so that by 2050 an estimated 13.8 million Americans will be living with AD (Alzheimer's Association, 2014a). MCI is of particular interest in this discussion because studies have shown that MCI increases the risk of progression to dementia, especially AD (Gauthier et al., 2006). In fact, in one longitudinal study researchers found that individuals with MCI were three times more likely to develop AD compared to
those without MCI (Bennett et al., 2002). Furthermore, the National Institute on Aging has identified MCI due to AD as one the three stages of AD in recent criteria (Sperling et al., 2011).

By identifying an early stage of AD, therapeutic and/or pharmacologic interventions can be developed and administered in hopes of delaying or preventing progression to AD (Bischkopf et al., 2002; Morris et al., 2001; Sherwin, 2000). In addition, if MCI is in fact a preclinical stage to AD, the delay or prevention of progression to AD may also be accomplished through even earlier interventions that target risk factors for MCI (Bischkopf et al., 2002). Although some studies have found significant relationships between MCI and common risk factors related to AD (i.e., cerebrovascular disease, age, vascular risk factors), many inconsistencies exist regarding those relationships (Buchman et al., 2005; Cherbuin et al., 2009; Decarli, 2003; Kivipelto et al., 2001; Lopez et al., 2003; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010). Body mass index (BMI) is one such variable in which results have varied from study to study. However, if modifiable factors like BMI can be confirmed to significantly increase the risk of MCI, AD, or other dementias, public health efforts could be better designed to target these health issues.

**STATEMENT OF THE PROBLEM**

The burden of AD is immense—with over 5 million people age 65 and older living with AD in the U.S. alone (Alzheimer's Association, 2014a). MCI has been shown to significantly increase the risk of dementia, especially AD. Because of this, MCI has now gained interest and support from researchers as a preclinical stage to AD (Gauthier et al., 2006). By studying risk factors for MCI, especially modifiable risk factors, public health efforts can be tailored to potentially delay or prevent the progression to AD altogether. However, there is a lack of consistency among studies investigating these risk factors. BMI, for instance, has been shown to be a risk factor in some studies, while protective in others.

**PURPOSE OF THIS STUDY**

The purpose of this study was to examine the association between BMI and MCI, after controlling for additional factors that may have affected the relationship between the two. As a secondary question, this study also investigated the relationship between BMI and
ethnicity and how this relationship could affect the risk of developing MCI. Specifically, this study investigated whether BMI was related to MCI among a cohort of older adults from San Diego County, a large metropolitan area with a high percentage of older adults. These subjects were recruited for participation in the University of California, San Diego (UCSD) Shiley-Marcos Alzheimer’s Disease Research Center (ADRC) Longitudinal Study. The results of the present study will help public health professionals better understand the BMI-MCI relationship, and specifically, identify whether BMI shows promise as a potential modifiable risk factor for MCI.

**GOALS AND HYPOTHESES**

1. How do baseline age, sex, ethnicity, family history of dementia, apolipoprotein E (APOE) ε4 presence, baseline BMI, history of diabetes, baseline Dementia Rating Scale (DRS) score, and baseline Mini-Mental Status Exam (MMSE) score associate with incident MCI?
   a. Sex and baseline MMSE score will not be significantly associated with incident MCI.
   b. Baseline age, APOE ε4 presence, baseline BMI, family history of dementia, baseline DRS score, and history of diabetes will be significantly associated with incident MCI.

2. After controlling for covariates, how does baseline BMI associate with incident MCI?
   a. Baseline BMI will be significantly associated with incident MCI after controlling for covariates. Specifically, a higher baseline BMI will predict incident MCI.

3. After controlling for covariates, how does the relationship (or interaction) between ethnicity and baseline BMI affect the risk of MCI?
   a. The relationship (or interaction) between ethnicity and baseline BMI will be significantly associated with incident MCI. Specifically among Hispanics, those who are obese or overweight will be more likely to develop MCI compared to those who fall into the underweight or normal BMI category. The same effect will be seen among non-Hispanics.

**THEORETICAL BASIS**

Although some studies have examined the relationship between BMI and AD, none have exclusively studied the relationship between BMI and MCI as a primary aim. Among studies that have investigated the association between BMI and AD, there are several inconsistencies. Some studies have found BMI to be positively associated with AD, while
others found BMI to be negatively associated with AD, or did not find a significant relationship at all (Beydoun, Beydoun, & Wang, 2008; Cronk, Johnson, & Burns, 2010; Driscoll et al., 2009; Tolppanen et al., 2014). In studies that found significant relationships between BMI and AD, generally higher midlife BMI was associated with increased risk of dementia and AD, whereas the role of late-life BMI was unclear (Beydoun et al., 2008; Tolppanen et al., 2014).

Because MCI is now being considered a risk factor for AD and has recently been identified as a potential preclinical stage to AD, it is possible that AD and MCI share similar, if not the same, risk factors (Bischkopf et al., 2002; Cherbuin et al., 2009; Morris et al., 2001; Sherwin, 2000; Sperling et al., 2011). Thus, if there is an association between BMI and AD or dementia, there may also be an association between BMI and MCI. Some of the lack of consistency in results of studies investigating the BMI-AD relationship may be due to the varied methods that have been used. This study allowed for control of multiple variables, including the typical demographics such as age and sex, but also important covariates such as history of diabetes. Furthermore, the present study drew data from a longitudinal study, which, by nature, allows for time-to-outcome analysis. These not only add value to our results, but also provide a model for studying other risk factors related to MCI.

**Basic Assumptions**

1. Results will be generalizable to the older adult population.
2. Information recorded in patient records was accurate.
3. Data was extracted from patient records and entered into the UCSD Shiley-Marcos ADRC database correctly.
4. The examinations and assessments used to identify MCI among patients were performed correctly.
5. The instruments used to identify MCI accurately capture MCI.
6. Subjects were truthful about their medical history.
7. Measurements acquired during subjects’ physical examinations, such as height and weight, were performed properly.

**Definition of Terms**

AD-Alzheimer’s disease
ADLs- activities of daily living; necessary everyday tasks, such as bathing, grooming, cooking (Alzheimer’s Association, 2014a)

ADRC- Alzheimer’s Disease Research Center

APOE ε4- apolipoprotein E, ε4 form

BMI- body mass index; measures a person’s relative body fat

Cardiovascular disease- disease of the heart and blood vessels; includes heart attack/cardiac arrest, atrial fibrillation, angioplasty/endarterectomy/stent, cardiac bypass procedure, pacemaker, and congestive heart failure (American Heart Association, 2011)

CDC- Centers for Disease Control and Prevention

Cerebrovascular disease- disease that results from problems with blood vessels in the brain; includes stroke and transient ischemic attack (NHS, 2013)

Diabetes- disease in which a person’s blood glucose levels are above normal; can result in other conditions such as heart disease and kidney failure (Centers for Disease Control and Prevention [CDC], 2014a)

DRS score- Dementia Rating Scale score

Ethnicity- of Hispanic origin or not of Hispanic origin

History of smoking- subject has smoked more than 100 cigarettes in his/her life

Hypertension- high blood pressure; results in increased risk of blood clots, plaque build-up, tissue and organ damage from narrowed/blocked arteries (American Heart Association, 2014)

IADLs- instrumental activities of daily living; tasks that are related to independent living, such as household chores, transportation, shopping (Alzheimer’s Association, 2014a)

MCI- mild cognitive impairment

MMSE score- Mini-Mental State Examination Score

UCSD- University of California, San Diego
CHAPTER 2
LITERATURE REVIEW

The purpose of this chapter is to provide an overview of what MCI is, including the epidemiology of MCI, diagnostic procedures, and clinical presentation. Risk factors for MCI are described, with particular focus on BMI. The chapter also explores the relationship of MCI with Alzheimer’s disease and other dementias (ADOD), which further validates the public health significance of this study.

OVERVIEW OF COGNITIVE IMPAIRMENT

Cognition refers to an individual’s ability to think, learn, and remember (National Institute on Aging, 2015). Good cognitive health is significant for one’s intuition, judgment, language skills, and memory (CDC, 2014b). Cognitive impairment can affect any of these processes, and it can manifest as, or be associated with, various diseases and conditions (CDC, 2014b). Some of these conditions include MCI, AD and other dementias, stroke, traumatic brain injury, and developmental disabilities (CDC, 2014b).

According to the CDC, there are over 16 million people in the U.S. living with cognitive impairment (CDC, 2009). The greatest risk factor for cognitive impairment is age (CDC, 2009). Thus, with our growing older population, the number of Americans affected with cognitive impairment is expected to increase dramatically (CDC, 2009). This not only places a huge economic burden on the U.S., but it also has a significant social impact. For example, people with cognitive impairment are three times more likely to be hospitalized compared to individuals with some other condition (CDC, 2009). Further, those with severe levels of cognitive impairment often require greater care as they lose the ability to live independently. This contributes to the social impact involved, as family and friends take on the role of caregiving. In fact, in 2009 it was estimated that 12.5 billion hours of unpaid care
were provided to those with cognitive impairment, with the majority of those hours coming from family and friends (CDC, 2009).

Although some cases of cognitive impairment can clearly be attributed to events such as traumatic injury, many cases are not fully understood. This makes prevention efforts difficult. Cognitive impairment associated with AD, for example, is especially unclear. Overall, cognitive impairment is a significant public health issue due to the many implications involved. With the aging population of the U.S., this problem will only become greater. Further research evaluating cognitive impairment and the conditions associated with it is necessary in order to further public health efforts.

**INTRODUCTION TO MILD COGNITIVE IMPAIRMENT**

As previously noted, cognitive impairment can manifest as several diseases and conditions (CDC, 2014b). Of these conditions, MCI is becoming of particular interest to researchers, many of whom are now considering MCI to be an early stage of AD and possibly other dementias (Bischkopf et al., 2002).

Although definitions of MCI vary, overall it is characterized by mild changes in thinking abilities that are noticeable to the person affected and to family and friends, without affecting the individual’s ability to carry out ADLs (Thies & Bleiler, 2013). Studies have shown that anywhere from 10% to 20% of people age 65 or older have MCI (Thies & Bleiler, 2013), with prevalence varying based off of what criteria for MCI was used (Bischkopf et al., 2002). Further, population-based studies have found that the prevalence of MCI is two times greater than that of dementia, with prevalence increasing after the age of 65 (Bischkopf et al., 2002). Similarly, incidence rates of MCI seem to increase with age (Bischkopf et al., 2002). Although few incidence studies have been conducted, Bischkopf et al. determined an average MCI incidence rate of 12 to 15 per 1000 person-years for people 65 years and older in their review of published MCI studies. Besides age, MCI may also be associated with race, sex, level of education, and cerebrovascular disease, among others (Cherbuin et al., 2009; Kivipelto et al., 2001; Lopez et al., 2003).
BACKGROUND AND DEFINITION OF MCI

In contrast to other forms of cognitive impairment that have been more well defined (e.g., AD), the definition and criteria for MCI has varied over time. One of the first attempts to identify a mild form of memory loss was termed age-associated memory impairment (AAMI), which was described as ‘memory loss that may occur in healthy, elderly individuals in the later decades of life’ (Crook et al., 1986). Criteria for AAMI include being 50 years or older, scoring one standard deviation below the mean for younger adults on a standardized memory test, and maintaining adequate intellectual functioning (Crook et al., 1986). Building off of the AAMI definition, the term ageing-associated cognitive decline (AACD) has also been widely used to describe mild forms of cognitive impairment. AACD does not contain an age restriction, and requires at least a six month duration of impairment, a report by the individual or reliable informant of cognitive decline, and a decline in any of the five cognitive domains (memory and learning, attention and concentration, thinking, language, and visuospatial functioning; Bischkopf et al., 2002). Other terms used to describe MCI include age-related cognitive decline (ARCD), mild cognitive disorder (MCD), minimal dementia, and cognitive impairment no dementia (CIND; Bischkopf et al., 2002; Gauthier et al., 2006).

Despite the number of definitions for MCI that have evolved over time, there is consensus that MCI should be considered its own diagnostic entity. One of the first major studies to examine MCI was that of Petersen et al. (1999), which compared individuals with MCI to both healthy controls and to those with AD through various clinical exams and assessments. Petersen et al. (1999) found that those with MCI differed from healthy controls in the area of memory, while other cognitive functions were similar. In contrast, memory performance was comparable between those with MCI and mild AD, but those with mild AD were more impaired in other cognitive functions (Petersen et al., 1999). These differences in performance among participants, particularly those with MCI, justified that MCI should be treated as its own diagnostic entity (Petersen et al., 1999).

Although historically there have been several different criteria for MCI, some of which are still used in current studies, it is now generally regarded as a syndrome characterized by cognitive decline that is not part of the normal aging process, yet does not interfere with an individual’s everyday activities, and does not constitute dementia (Gauthier
et al., 2006; Petersen, 2004). In other words, those with MCI show some kind of cognitive decline that can be confirmed from their patient history and/or measured through objective cognitive tasks, are neither normal nor demented, and can still carry out ADLs as well as IADLs (Winblad et al., 2004).

**DIAGNOSIS OF MCI**

Further recognition of the heterogeneity of MCI has also led to suggested sub-classifications, which include a-MCI vs. na-MCI and single domain (or single cognitive deficit) vs. multiple domain (or multiple cognitive deficits) MCI (Petersen, 2004; Petersen et al., 2001). These differences can further complicate the diagnostic process, however several recommendations exist to help guide clinicians during this process (Refer to Figure 1; Gauthier et al., 2006; Petersen, 2004; Winblad et al., 2004).

![Figure 1. Flow chart of the decision process for making diagnosis of MCI and subtypes of MCI. Source: Petersen, R. C. (2004). MCI as a diagnostic entity. Journal of Internal Medicine, 256(3), 183–194.](image-url)

First, the clinician should refer to the general criteria for MCI – that the person (1) does not have normal cognitive function for their age, (2) is not demented, (3) does have cognitive decline, and (4) can essentially carry out normal activities (including ADLs and
IADLs; Gauthier et al., 2006; Petersen, 2004; Winblad et al., 2004). The first two criteria are based off of the clinician’s judgment after examining the patient’s history and administering a mental status exam, assuming that the patient in question or another individual expresses concern about the patient’s cognitive health (Petersen, 2004; Winblad et al., 2004). Once it is determined that the patient is neither normal nor demented, cognitive decline must be confirmed through a more thorough history from the patient and, if possible, a close relative or friend (Petersen, 2004; Winblad et al., 2004). Cognitive decline may also be measured through objective cognitive tasks and/or evidence of decline over time on objective neuropsychological tests (Winblad et al., 2004). The last criteria would then require the clinician to judge whether or not the cognitive decline confirmed in step 3 is significant enough to impair the individual’s everyday activities (Petersen, 2004; Winblad et al., 2004). If so, the person would be considered to have very mild dementia, otherwise MCI would be an appropriate classification (Petersen, 2004; Winblad et al., 2004).

After confirming general criteria for MCI, the clinician may also identify the subtype of MCI afflicting the patient – amnestic vs. non-amnestic and single domain vs. multiple domain (Petersen, 2004; Winblad et al., 2004). This is accomplished through comprehensive cognitive testing, including neuropsychological testing (Petersen, 2004; Winblad et al., 2004). If testing reveals significant memory impairment, this indicates a-MCI (Petersen, 2004). Otherwise if significant memory impairment is not found, it is implied that the individual has na-MCI (Petersen, 2004). The last step is to determine if the individual has a single impairment only, or impairment in multiple cognitive domains (Petersen, 2004; Winblad et al., 2004). Among those with a-MCI, the clinician would need to determine if the impairment just involves memory (a-MCI, single domain) or if cognitive domains (e.g., language, attention/executive function, visuospatial skills) are impaired in addition to memory (a-MCI, multiple domain; Petersen, 2004; Winblad et al., 2004). A similar approach would be applied to those with na-MCI to determine if a single non-memory domain is impaired (na-MCI, single domain), or if multiple domains are affected (na-MCI, multiple domain; Petersen, 2004; Winblad et al., 2004).
**MCI: Relationship with AD and Dementia**

Within the field of aging and dementia, increasing efforts are being made to characterize the earlier stages of impairment on the cognitive spectrum of normal aging to AD (Petersen, 2004; Petersen et al., 2001). Recently, further interest in identifying an early stage of AD has emerged with the discovery of the long preclinical phase of AD of up to 7 years (Elias et al., 2014). MCI is at the forefront of many of these studies examining preclinical AD; in fact, MCI has consistently been shown to increase the risk of progression to dementia, especially AD (Gauthier et al., 2006). Increasing acceptance of this notion is evident in recent criteria proposed by the National Institute on Aging, which identifies MCI due to AD as one of the three stages of AD (Sperling et al., 2011).

The challenge of studying the relationship between MCI and dementia, or MCI and AD specifically, stems from the heterogeneity of MCI itself. While a-MCI has generally been regarded as the subtype that most commonly leads to AD, many studies often do not make this distinction when examining the conversion from MCI to AD (Petersen et al., 2006). In addition, it is less clear how other MCI subtypes may be associated with AD or dementia in general (Petersen, 2004). Petersen et al. suggests the following schema to demonstrate relationships between the most common forms of dementia and MCI subtypes, however this is an area that needs additional research (Refer to Figure 2).
Figure 2. Proposed relationships for MCI subtypes based on presumed etiology (AD=Alzheimer’s disease, DLB=Dementia with Lewy Bodies, FTD=Frontotemporal Dementia, VaD=Vascular Dementia, Depr=Depression)


Given the heterogeneity of MCI, the actual rate of conversion of those with MCI to dementia varies among studies, with the majority of conversion rates reported anywhere between 4-36% (Bennett et al., 2002). However, a longitudinal study conducted by the Mayo ADRC found that 12% of MCI subjects followed for 3-6 years progressed to dementia annually and at the end of the 6-year study, an estimated 80% converted to dementia overall (Petersen et al., 2001). Other studies have also found that up to 15% of individuals with MCI who contact their physicians for an exam because of concerns about their symptoms will go on to develop dementia each year, and almost half of those individuals will develop dementia in 3 or 4 years (Petersen et al., 1999). Similarly, conversion rates between MCI and AD also vary across studies. In one attempt to explore the epidemiology of MCI, researchers found that 23% of MCI subjects who survived 10 years of follow-up after meeting MCI criteria progressed to AD (Ganguli, Dodge, Shen, & DeKosky, 2004). Yet, several researchers and leaders within the dementia field suggest that the majority of MCI cases, especially the amnestic type, represent early AD, and a more appropriate diagnosis may be “MCI due to AD” (Albert et al., 2011; Sperling et al., 2011). Conversion rates also vary based on criteria...
used for different types of dementia, sample size, follow-up period, whether the study sample was clinical or community-based, and other variables that were controlled for in the analysis (Bennett et al., 2002; Sosa-Ortiz, Acosta-Castillo, & Prince, 2012).

It is also important to note that a perfect conversion rate from MCI to dementia is not expected - some individuals with MCI, particularly those without memory problems (non-amnestic MCI), can experience improved cognition and even revert back to normal cognitive status (Ganguli et al., 2011). Researchers are still exploring why not all MCI cases progress to AD or other dementias. Particularly, studies are looking into biomarker testing that could possibly identify physiological processes associated with AD or other dementias in those with MCI (Thies & Bleiler, 2013). Reports of relative risk of MCI and AD are less common, however in a longitudinal study conducted by Bennett et al. (2002), researchers found that individuals with MCI were an estimated three times more likely to develop AD compared to those without impairment, at an average follow-up period of 4.5 years.

**SIGNIFICANCE OF THE MCI-AD RELATIONSHIP**

By identifying MCI as a stage prior to clinically probable or confirmed AD, therapeutic and/or pharmacologic interventions can be developed and administered in hopes of delaying or preventing progression to AD (Bischkopf et al., 2002; Morris et al., 2001; Sherwin, 2000).

Globally, there was an estimated 35.6 million people living with dementia in 2010 (Sosa-Ortiz et al., 2012). This number is projected to double every 20 years, so that by 2030, 65.7 million people will be living with dementia (Sosa-Ortiz et al., 2012). Although dementia affects people in different ways depending on what subtype is present, all dementias are generally characterized by neuronal loss or malfunction and changes in memory, behavior, and thinking skills (Thies & Bleiler, 2013).

AD is considered the most common form of dementia, accounting for 60-80% of all dementia cases (Mayeux & Stern, 2012; Nowrangi, Rao, & Lyketsos, 2011; Reitz, Brayne, & Mayeux, 2011). In the U.S, an estimated 5.2 million Americans had AD in 2013, which was comprised of 5.0 million people aged 65 years and older and an additional 200,000 individuals younger than 65 who had an earlier onset of AD (Alzheimer’s Association, 2006; Hebert, Weuve, Scherr, & Evans, 2013; Thies & Bleiler, 2013). Locally, AD is the fifth
leading cause of death in California and the third leading cause of death in San Diego County (Alzheimer’s Association, 2009; County of San Diego, 2015). In 2012, an estimated 60,000 San Diegans were living with ADOD, accounting for 8% of the population (County of San Diego, 2015). If current trends continue, by 2030 nearly 94,000 residents in San Diego County will be living with ADOD, a 56% increase from 2012 (County of San Diego, 2015). Common signs and symptoms of AD include memory loss that disrupts daily life, challenges in planning or solving problems and completing familiar tasks, confusion with time or place, and impaired judgment, among others (Thies & Bleiler, 2013).

The social, economic, and personal burden involved with AD and other dementias is immense – not only does the individual suffering from ADOD experience daily challenges but those caring for the individual often encounter their own difficulties. In 2012, over 15 million family members and other caregivers provided an estimated 17.5 billion hours of unpaid care to people with ADOD, valued at over $216 billion (Thies & Bleiler, 2013). In San Diego County that year, nearly 137,000 San Diegans provided 156 million hours on unpaid care to those suffering from ADOD, valued at $1.94 billion (County of San Diego, 2015). Caregivers often experience increased emotional stress, depression, and financial hardship, which lead to poor health outcomes (Thies & Bleiler, 2013). In fact, health care costs to caregivers in San Diego County were $75.4 million in 2012 (County of San Diego, 2015).

Furthermore, those living with ADOD place a burden on the health system. Those living with ADOD have more hospital stays, skilled nursing facility stays, and home health care visits compared to older individuals without ADOD (Bynum, 2011; Thies & Bleiler, 2013). Currently, Medicare payments for beneficiaries with ADOD are three times higher compared to those without these conditions, and Medicaid payments are 19 times higher (Thies & Bleiler, 2013). By 2050, there will be an estimated $1.2 trillion in costs for health care, long-term care, and hospice for those living with ADOD (Thies & Bleiler, 2013). There is also an increasing demand for health care professionals, especially within geriatrics, given that the U.S. only has an estimated half of the geriatricians it currently needs (Eldercare Workforce Alliance, 2012).

Currently, the specific causes of AD are still being explored. However, there are known risk factors for AD that are unmodifiable; these include age, family history of
dementia, and genetics (Alzheimer’s Association, 2014b). Current research is focused on identifying preventable risk factors, and many studies have found that the risk of AD is increased by conditions that damage the heart or blood vessels, such as high blood pressure, heart disease, stroke, diabetes, and high cholesterol (Alzheimer’s Association, 2014b). By studying preventable risk factors as well as identifying a preclinical stage in which to target therapeutic interventions, we can better understand how to target this public health issue.

**RISK FACTORS RELATED TO MCI**

In addition to targeting MCI as an early stage for therapeutic interventions, the delay or prevention of progression to AD may also be potentially accomplished through earlier interventions that target risk factors for MCI (Bischkopf et al., 2002; Cherbuin et al., 2009; Morris et al., 2001; Sherwin, 2000). Some factors that have been shown to be significantly associated with MCI or AD include age, ethnicity, sex, level of education, cerebrovascular disease, vascular risk factors (i.e., systolic blood pressure, serum cholesterol level), BMI, diabetes, genetics (i.e., family history of dementia, APOE ε4 status), and depression (Buchman et al., 2005; Cherbuin et al., 2009; Decarli, 2003; Kivipelto et al., 2001; Lopez et al., 2003; Plassman et al., 2010). For this analysis BMI will be the primary risk factor analyzed, with a secondary interest in ethnicity.

Demographic characteristics of interest include age, sex, and ethnicity. Generally, the risk of cognitive impairment, including MCI and AD, increases with age (Cherbuin et al., 2009; Ganguli, Dodge, Chen, Belle, & DeKosky, 2000). An MCI incidence rate of 54 per 1000 person-years has been estimated for individuals 75 years and older (Paykel et al., 1994), a rate much higher than the estimated incidence of 12 to 15 per 1000 person-years for those aged 65 years and older (Bischkopf et al., 2002). The effect of sex on MCI risk is less clear; one study suggests that in contrast to what occurs in dementia, men are more likely to develop MCI compared to women (Ganguli et al., 2000). However, results vary based on methodology (Bischkopf et al., 2002). There is also little known regarding MCI risk among ethnic groups (Rose, 2005; Tang, 1998; Unverzagt et al., 2001). Yet, research has shown that Hispanics and blacks are at an increased risk of developing AD, which suggests that a similar relationship with MCI may exist among those ethnic groups (Rose, 2005; Tang, 1998; Unverzagt et al., 2001). In fact, studies have found that Hispanics are 1.5 to 2 times more
likely to develop AD compared to non-Hispanic whites (Fitten, Ortiz, & Ponton, 2001; Thies & Bleiler, 2013).

Other covariates of interest include presence of an APOE ε4 allele, history of diabetes, and family history of dementia, all of which have been found to be significantly associated with AD and therefore may also be related to MCI. The APOE gene is essential in providing the blueprint for protein that carries cholesterol in the bloodstream (Thies & Bleiler, 2013). Everyone inherits one APOE allele from each parent, which can be either an ε2, ε3, or ε4 allele (Thies & Bleiler, 2013). Having a copy of the ε3 form does not seem to affect AD risk, whereas having the ε2 form may decrease one’s risk (Thies & Bleiler, 2013). Having one copy of the ε4 form, however, not only increases AD risk but also increases the risk of developing the disease at a younger age (Thies & Bleiler, 2013). Similarly in several MCI studies, participants with MCI were more likely to carry an APOE ε4 allele compared to cognitively normal subjects (Grundman et al., 2004; Lopez et al., 2003). History of diabetes has also been found to be associated with MCI and AD (Lopez et al., 2003; Manly et al., 2008; Profenno, Porsteinsson, & Faraone, 2010; Thies & Bleiler, 2013). In a meta-analysis examining the relationship between AD and several risk factors, researchers found a pooled effect size for diabetes of 2.06 after adjusting for other vascular factors, stroke, and APOE ε4 (Profenno et al., 2010). Individuals with a family history of dementia have been reported to increase the risk of AD as well, with studies reporting a higher risk for those who have more than one first-degree relative with AD (Lautenschlager et al., 1996; Mayeux, Sano, Chen, Tatemichi, & Stern, 1991; Thies & Bleiler, 2013).

MMSE score and DRS score have also been included as covariates in several MCI and ADOD studies. Both the MMSE and DRS are tools used to assess an individual’s cognitive status (Hohl, Grundman, Salmon, Thomas, & Thal, 1999). The MMSE is a 30-item screening tool that assesses orientation in time and place, attention and concentration, immediate and delayed recall, constructional abilities, and the use of language (Hohl et al., 1999). The DRS includes five subscales – attention, initiation and perseveration, construction, conceptualization, and memory – and has been described as being able to provide more information about a patient’s cognitive status compared to other widely used instruments (Hohl et al., 1999; Monsche et al., 1995). Cut-points for these assessments can vary from study to study, but generally an MMSE score of ≥24-27 out of 30 and DRS score
of $\geq 130$ out of 144 indicates normal cognitive status (Alzheimer’s Society, 2012; Ganguli et al., 2004; Grundman et al., 2004; Hohl et al., 1999).

**A DESCRIPTION OF BODY MASS INDEX (BMI)**

BMI has been recognized as the standard for measuring weight problems in individuals, especially obesity (National Heart, Lung, and Blood Institute [NHLBI], 1998). Although BMI does not measure body fat directly, it does serve as an important screening tool for clinicians because it is inexpensive and easy to use (CDC, 2014c; Prentice & Jebb, 2001). BMI is calculated by dividing a person’s weight in pounds by their height in inches squared and multiplying a conversion factor of 703; the conversion factor is used when not using metric system measurements (CDC, 2014c). The standard categories associated with BMI ranges include the following: underweight for a BMI below 18.5, normal for a BMI between 18.5 and 24.9, overweight for a BMI between 25.0 and 29.9, and obese for a BMI of 30.0 or above (CDC, 2014c). Although the present study is examining BMI as a predictor for MCI, research has also found BMI to be associated with hypertension, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, and some cancers (NHLBI, 1998).

**THE RELATIONSHIP BETWEEN MCI AND BMI**

Despite evidence identifying several risk factors for MCI, there is limited research for other risk factors, such as BMI. Preliminary research on BMI has found that it may be associated with MCI (Cherbuin et al., 2009; Kivipelto et al., 2001) however, additional research could be used to further strengthen this finding. Due to limited research on the relationship between BMI and MCI, the association between BMI and AD or dementia in general will primarily be examined in this section in an effort to provide background for the current study. If there is an association between BMI and AD, or dementia in general, it is possible that BMI may also be associated with MCI (Bischkopf et al., 2002; Cherbuin et al., 2009; Morris et al., 2001; Sherwin, 2000).

There are several proposed theories that attempt to explain the relationship between BMI and cognitive impairment. One suggested mechanism is that high BMI increases the risk of comorbidities, such as cardiovascular disease or diabetes, and it is these comorbidities
that increase the risk of AD or other dementias (Tolppanen et al., 2014). However, several studies have found BMI to be significantly related to AD and other dementias independently of comorbidities (Buchman et al., 2005; Profenno et al., 2010; Whitmer, Gunderson, Quesenberry, Zhou, & Yaffe, 2007). Imaging studies have also suggested that higher BMI is associated with neuronal abnormalities characteristic of AD and other dementias, such as white matter lesions and decreased global and local brain volume (Tolppanen et al., 2014). For example, one study found that higher BMI was associated with lower brain volumes in frontal, temporal, parietal, and occipital lobes in both those with AD and those with MCI (Ho et al., 2010). These findings are also consistent among older adults without existing cognitive deficits (Gazdzinski, Kornak, Weiner, & Meyerhoff, 2008). Furthermore, higher BMI has been associated with a higher rate of atrophy progression (Enzinger et al., 2005).

Other proposed mechanisms focus on the direct link between AD and adiposity, as opposed to the indirect measure of adiposity using BMI or waist circumference; these include hyperinsulinemia, advanced glycosylation end products (AGEs), and adipokines and cytokines (Luchsinger & Gustafson, 2009). Insulin has been linked to the clearance of amyloid in the brain, which has been considered a major factor in neuronal destruction associated with AD (Farris et al., 2003; Selkoe, 2000). Hyperinsulinemia, a condition related to insulin resistance and triggered by high adiposity, may inhibit brain insulin production and result in impaired amyloid clearance, therefore increasing the risk of AD (Reger et al., 2006; Shanik et al., 2008). High adiposity may also lead to impaired glucose intolerance, producing AGEs that have been linked to plaques and neurofibrillary tangles, which are pathologic indicators of AD (Cummings, 2004). The role that adipokines and inflammatory cytokines is less clear, however some studies suggest that they may have direct effects on brain regions implicated in those with dementia (Alzheimer’s Disease International, 2014; Luchsinger & Gustafson, 2009). For example, higher levels of the adipokine leptin has been shown to be associated with a lower incidence of dementia and AD and higher brain volume (Lee, 2011).

Numerous epidemiological studies have been conducted in an attempt to investigate the relationship between BMI and incident AD and dementia. Several studies have found that higher midlife BMI has been associated with an increased risk of dementia and AD (Fitzpatrick et al., 2009; Tolppanen et al., 2014; Whitmer et al., 2007). Studies taking into account the life course of the BMI-AD/dementia relationship have especially been valuable,
particularly those that are longitudinal in nature (Tolppanen et al., 2014). In one such study, the Cardiovascular risk factors, Aging, and Dementia (CAIDE) study, the associations between midlife BMI and late-life BMI and incident dementia were investigated among 1,304 participants over a 26 year follow-up period (Tolppanen et al., 2014). Interestingly, the relationship between BMI and incident dementia followed a U-shaped curve – higher BMI at midlife but lower BMI at late-life led to an increased risk of developing dementia (Tolppanen et al., 2014). As an additional strength to this finding, researchers found these associations to be independent of additional obesity-related co-morbidities (Tolppanen et al., 2014). Other studies examining BMI and incident dementia and AD found similar results, with the proposed effects sometimes varying by BMI; for example, one study found BMI>25 at late-life to be protective (Atti et al., 2008), whereas another found BMI>20 at late-life to be sufficient in reducing dementia risk (Fitzpatrick et al., 2009).

However, according to the 2014 World Alzheimer Report on dementia and risk reduction, results regarding the association between BMI and dementia are often weak, inconsistent, and subject to bias (Alzheimer’s Disease International, 2014). For example, the Cardiovascular Health Study found that individuals who were obese at midlife had a 39% increased risk of developing dementia and 17% increased risk of developing AD compared to those who fell within the normal BMI category (Fitzpatrick et al., 2009). However, these findings may be flawed given that midlife BMI was determined based on participants’ recollection of how much they weighed at age 50 (Fitzpatrick et al., 2009). In addition, there are several studies that have ascertained BMI and dementia data through linkage to hospital discharge and mortality data, which is subject to bias given that individuals with higher BMI are more likely to be in contact with formal health services (Alzheimer’s Disease International, 2014). Similar discrepancies exist among studies examining the relationship between BMI and cognitive decline (Cronk et al., 2010).
CHAPTER 3

METHODS

STUDY DESIGN

This is an analysis of data obtained from the UCSD ADRC. The ADRC began in 1984 as one of the original five of the now thirty federally funded AD Centers in the U.S. There are several research studies conducted by the UCSD ADRC. The present analysis drew data from the ADRC Longitudinal Study, an ongoing research study that annually follows individuals with and without memory problems. The goals of the ADRC Longitudinal Study include gaining a greater understanding of normal aging versus dementia, increasing diagnostic accuracy of different forms of dementia, and examining the clinical symptoms and progression to dementias as well as their effects on brain pathology.

STUDY POPULATION

The ADRC Longitudinal study has continuously recruited participants with and without memory impairment beginning in 1985. The majority of patients with AD or other dementias were referred by UCSD or community physicians, the Alzheimer’s Association, or local AD care centers. Individuals with MCI were recruited largely from the ADRC Memory and Aging Project (MAP) and Memory Screening Clinic. These programs conduct psychometric and functional screens for community-based elderly individuals who have memory concerns or for elderly individuals with cognitive complaints who are referred by their primary care physician. From 1985 to August 2013, almost 2,200 individuals had been enrolled and studied in the ADRC longitudinal cohort: 1,270 AD, 445 controls, 171 MCI, 75 Parkinson’s Disease/Parkinson’s Disease Dementia (PD/PDD), 106 Dementia with Lewy Bodies (DLB), 57 Frontotemporal Dementia (FTD), and 73 others.

The present analysis was restricted to subjects who were recruited into the cognitively normal cohort (Normal Controls), excluding those who had AD, other dementias, MCI, or
other memory deficits at the time of enrollment. To be considered a Normal Control, the subject also must have functioned normally and independently at the time of enrollment, which was indicated by their health history and an assessment of IADLs and ADLs. General inclusion criteria for all participants (both patients and controls) required that subjects were ambulatory, community-residing volunteers who spoke English or Spanish (to enable full cooperation with neuropsychological testing and other evaluation procedures). Exclusion criteria for all participants included current alcohol or drug abuse, mental retardation or developmental delay, major psychoses (e.g., schizophrenia), significant sensory impairment (e.g., blindness, deafness), major systemic diseases or medical conditions (e.g., chronic renal failure, chronic hepatic disease, cancer), or strokes that cause gross speech, motor, somatosensory, or visual impairment. The final sample size included 339 Normal Controls, after selecting for various characteristics (Refer to Figure 3).

![Flowchart](image)

**Figure 3. Sample size selection, given analysis criteria.**

Elderly Normal Control participants were recruited through educational presentations at community health fairs, community centers, and retirement facilities. Several large, multi-step retirement facilities in San Diego were a main source for control subjects. In addition, controls were identified through advertisement in newsletters (e.g., Alzheimer Association)
and on radio, and recruitment of spouses of patients. A knowledgeable informant was required for all controls and patients. Autopsy consent and consent for imaging (unless contra-indicated) was required for enrollment in almost all cases. Consent for lumbar puncture (LP) was highly encouraged.

**DATA COLLECTION**

Data for this study was obtained from both the baseline visit and the annual follow-up visits for participants enrolled in the ADRC Longitudinal Study. Each year, participants received a four hour annual exam that included an exhaustive neuropsychometric battery and a formal clinical exam by a neurologist. Examples of assessments included in the battery were the DRS and MMSE. Through these assessments, clinicians evaluated the participant’s global mental status, attention, language, verbal and nonverbal memory, executive functions, visuospatial abilities, psychomotor skills, and premorbid intellectual status. Taking all results into account, a consensus panel composed of at least two neurologists, a neuropsychologist, and a nurse practitioner made note of the participant’s cognitive status (i.e., possible AD, MCI, normal cognitive status, etc.) at that follow-up time. At baseline, participants also completed a comprehensive interview regarding their demographics, medical history, and current medications they were taking. The outcome/event and time-to-event variables for this study were determined using follow-up data. Information from baseline visits was used to obtain data on the main predictors, BMI and ethnicity, as well as covariates. The following variables were included in this analysis.

**OUTCOME**

For this analysis, the outcome was referred to as incident MCI. However, subjects considered to meet the outcome also included those who received an “at risk for AD” diagnosis. Formal clinical diagnostic criteria for MCI as implemented by the National Alzheimer Coordinating Center were introduced in 2004 (Winblad et al., 2004). Prior to 2004, a consensus diagnosis of "At Risk for AD" was used as a proxy for MCI. These were subjects judged to have a neuropsychometric profile consistent with early AD, but who were functioning relatively independently in ADL and who did not meet criteria for dementia. Among those that did receive an MCI diagnosis once criteria were implemented, subjects
who specifically had the a-MCI diagnosis were included and those with na-MCI were excluded in this analysis. The general term used to incorporate these diagnoses and describe the outcome was “MCI.”

**RISK FACTORS**

The main predictor of interest in this study was baseline BMI. BMI was first calculated using height and weight variables. Because BMI is typically used to measure whether an individual is overweight or obese, it was then categorized based on the following standard groupings: <18.5 underweight, 18.5-24.9 normal, 25.0-29.9 overweight, and ≥30.0 obese. For the purposes of this analysis, the underweight and normal categories were combined given that there were only 3 (<1.0%) individuals that fell within the underweight category. Thus, the final categories were underweight or normal, overweight, and obese. The secondary predictor of interest was ethnicity, which was dichotomized as Hispanic or non-Hispanic. Height, weight, and ethnicity were recorded at the baseline visit.

**COVARIATES**

Demographic variables included in the study were also baseline characteristics and included age and sex. Age was a continuous variable measured in 1 year increments, and sex was a dichotomous variable with the standard male and female categories. In addition, the analysis controlled for the following covariates based on a review of past studies involving BMI and cognitive impairment: presence of an APOE ε4 allele, history of diabetes, family history of dementia, MMSE score, and DRS score. APOE ε4 presence, history of diabetes, and family history of dementia were all dichotomous variables with yes and no categories. DRS score and MMSE were continuous variables measured in 1 unit increments. The APOE ε4 variable was calculated using the original APOE variable from the dataset, which listed a two digit number that represented the two types of alleles the participant inherited from their parents. For example, a participant with an APOE value of 24 or 42 indicated that he or she inherited one copy of the APOE ε2 allele and one copy of the APOE ε4 allele. The APOE ε4 variable in this analysis was dichotomized as yes or no, with a yes indicating that the participant had at least one copy of the APOE ε4 allele. Family history of dementia was
determined based on whether the participant had either a sibling or a parent with history of dementia.

For the Cox proportional hazards analysis, time-to-outcome was calculated as time (in years) to the first annual exam with diagnosis of MCI or “at risk for AD”. Subjects who reached a competing neurocognitive endpoint, such as vascular dementia or mixed vascular-AD dementia, were censored at the time of the first visit with a non-normal diagnosis; subjects who remained cognitively normal throughout the study period were censored at the time of their last clinical exam.

**Statistical Analysis**

All analyses were performed using SAS Studio version 3.2 (SAS Institute Inc., Cary, NC). Descriptive analyses were performed to obtain information on participant demographics and the factors of interest in this study. To estimate the risk of MCI associated with BMI, survival analysis methods (Kaplan-Meier and Cox Proportional Hazards) were used. Kaplan-Meier curves were constructed for the main predictors, BMI category and ethnicity, and the log-rank test was used to determine significant differences in survival (non-MCI outcome) across BMI and ethnicity categories. Unadjusted hazard ratios and their corresponding 95% confidence intervals were also reported in examining the relationship between each variable and MCI risk. Those variables that were tested and yielded a $p$-value of less than 0.05 in univariate analyses were included in the multivariable analysis.

Using Cox regression analysis, a multivariable model was determined that explained the relationship between BMI category and MCI while allowing for the adjustment of covariates. Variables were entered into the multivariable model if their survival bivariate $p$-value was less than 0.05 and were kept in the model based on that same value. The main predictors in question, BMI category and ethnicity, entered the model regardless of bivariate results, followed by individual additions of covariates that were determined statistically significant in the bivariate analysis. BMI category and ethnicity always remained in the model regardless of insignificance in any of the modeling steps. Adjusted hazard ratios, 95% confidence intervals, and $p$-values were reported for variables in the final multivariable model. For the purpose of this analysis, the proportional hazards assumption was tested and verified for each variable.
CHAPTER 4

RESULTS

From 1985 to August 2013, 445 Normal Controls, individuals without existing cognitive impairment at the time of enrollment, were enrolled in the UCSD Shiley-Marcos ADRC Longitudinal Study. Of the 445 subjects enrolled in the study, 339 were included in the analysis based on available data for selected variables. Table 1 displays the selected demographic and health characteristics of these controls. Overall, the study population consisted mostly of females (60.2%) and subjects were mainly non-Hispanic (75.2%). The population was also older, with a mean age of 72 years. Based on established BMI categories, of the 339 participants, 137 (40.4%) were considered underweight or normal, 131 (38.6%) were considered overweight, and 71 (20.9%) were considered obese. Similarly, the average BMI of subjects was 26.5, which falls into the overweight category according to established standards. More than half (56.3%) of participants had a family history of dementia. Aligned with this number, almost a third (28.9%) had the presence of an APOE ε4 allele, a genotype which increases the risk for AD. A smaller percentage had a history of diabetes (7.1%). Mean baseline scores for both the DRS and MMSE were also included, which were 138 and 29, respectively. Both scores indicate normal cognitive health, which is consistent with sample selection criteria for this analysis. Among the 339 participants, 59 (17.4%) developed MCI during the study period. Of those who developed MCI, the average time-to-incident MCI was 8.9 years.
Table 1. Selected Demographic and Health Characteristics of Normal Controls at Baseline in the UCSD Shiley-Marcos ADRC Longitudinal Study, 1985-2013 (N=339)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%), n=339</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body Mass Index</strong></td>
<td></td>
</tr>
<tr>
<td>Underweight or Normal†</td>
<td>137 (40.4)</td>
</tr>
<tr>
<td>Overweight‡</td>
<td>131 (38.6)</td>
</tr>
<tr>
<td>Obese ₢</td>
<td>71 (20.9)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>84 (24.8)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>255 (75.2)</td>
</tr>
<tr>
<td><strong>APOE ε4 Allele</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>98 (28.9)</td>
</tr>
<tr>
<td>No</td>
<td>241 (71.1)</td>
</tr>
<tr>
<td><strong>Family history of dementia</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>191 (56.3)</td>
</tr>
<tr>
<td>No</td>
<td>148 (43.7)</td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24 (7.1)</td>
</tr>
<tr>
<td>No</td>
<td>315 (92.9)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>204 (60.2)</td>
</tr>
<tr>
<td>Male</td>
<td>135 (39.8)</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>71.7 (8.4)</td>
</tr>
<tr>
<td>DRS Score</td>
<td>137.8 (5.2)</td>
</tr>
<tr>
<td>MMSE Score</td>
<td>29.2 (1.1)</td>
</tr>
</tbody>
</table>

To investigate the potential interaction between BMI and ethnicity, the proportion of MCI among ethnicities was stratified by BMI category (Refer to Figure 4). As shown in the figure, a higher percentage of Hispanics who fell within the underweight or normal BMI category (20.8%) converted to MCI compared to those in the overweight (17.2%) or obese (9.7%) categories. In contrast, among non-Hispanics a greater proportion converted to MCI if they were obese (25.0%) or overweight (18.6%) compared to underweight or normal (15.0%).
Bivariate Analysis

According to bivariate analysis results displayed in Table 2, the main predictor of interest, BMI category, was not significantly associated with MCI risk ($p=0.6749$). Neither being overweight ($p=0.7614$) nor obese ($p=0.3779$) appeared to be significantly related to developing MCI. In addition, there was no significant difference in MCI risk between Hispanics and non-Hispanics prior to adjusting for covariates ($p=0.6985$). These results were confirmed through log-rank tests during the construction of Kaplan Meier survival curves for each of these key predictors (Refer to Figures 5 and 6).
Table 2. Bivariate Analysis Between Incident MCI and Selected Baseline Characteristics of Normal Controls in the UCSD Shiley-Marcos ADRC Longitudinal Study, 1985-2013 (N=339)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)†</th>
<th>Unadjusted Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body Mass Index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>13 (22.03)</td>
<td>1.36</td>
<td>0.68-2.72</td>
</tr>
<tr>
<td>Overweight</td>
<td>24 (40.68)</td>
<td>1.09</td>
<td>0.61-1.95</td>
</tr>
<tr>
<td>Underweight or Normal‡</td>
<td>22 (37.29)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>13 (22.0)</td>
<td>0.89</td>
<td>0.48-1.65</td>
</tr>
<tr>
<td>Non-Hispanic‡</td>
<td>46 (78.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.09</td>
<td>1.05-1.13</td>
<td></td>
</tr>
<tr>
<td><strong>APOE ε4 Presence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (47.5)</td>
<td>2.20</td>
<td>1.34-3.77</td>
</tr>
<tr>
<td>No‡</td>
<td>31 (52.5)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>DRS Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.98</td>
<td>0.93-1.02</td>
<td></td>
</tr>
<tr>
<td><strong>MMSE Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.03</td>
<td>0.80-1.33</td>
<td></td>
</tr>
<tr>
<td><strong>Family history of dementia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 (62.7)</td>
<td>1.27</td>
<td>0.75-2.16</td>
</tr>
<tr>
<td>No‡</td>
<td>22 (37.3)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (6.8)</td>
<td>1.61</td>
<td>0.58-4.49</td>
</tr>
<tr>
<td>No‡</td>
<td>55 (93.2)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37 (62.7)</td>
<td>1.04</td>
<td>0.61-1.77</td>
</tr>
<tr>
<td>Male‡</td>
<td>22 (37.3)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Key: *p<.05; **p<.005; ***p<.0005
† n=59 Normal Controls with MCI outcome
‡ Indicates reference category
Figure 5. Kaplan-Meier survival curves for Normal Controls - an examination of the relationship between BMI category and MCI risk ($p=0.6735$, log-rank test, unadjusted). Survival displayed as years post enrollment.
Age, sex, family history of diabetes, APOE ε4 presence, DRS score, and MMSE score were examined as potential covariates. Among these, age was found to be significantly associated with MCI risk ($p<0.0001$), not adjusting for other variables. For every 1 year increase in age, the risk of developing MCI increases by a factor of 1.09 (95% CI 1.05-1.13). In addition, presence of the APOE ε4 allele was significantly associated with MCI risk ($p=0.0022$). Those who have a copy of the APOE ε4 allele are 2.24 times more likely to develop MCI compared to those who do not have a copy of the allele (95% CI 1.34-3.77). Sex, family history of diabetes, DRS score, and MMSE score did not have individual significant associations with MCI risk.
MULTIVARIABLE ANALYSIS

BMI category (overweight vs. normal/underweight, obese vs. normal/underweight), ethnicity (Hispanic vs. non-Hispanic), age (continuous), and APOE ε4 presence (yes vs. no) were included in the multivariable analysis. As the main predictors in question, BMI and ethnicity were examined during this analysis regardless of insignificance identified during bivariate analyses. The covariates age and APOE ε4 entered the model given that their bivariate p-values met the p<0.05 requirement. Models using Cox proportional hazards are reported in Table 3, with the results of the multivariable analyses displayed in Tables 4 and 5.

Table 3. Set of Cox Regression Models that Display the Fitted Relationship Between BMI and MCI, while Controlling for Selected Baseline Characteristics of Normal Controls in the UCSD Shiley-Marcos ADRC Longitudinal Study, 1985-2013 (N=339)

<table>
<thead>
<tr>
<th>β (Std. Error)</th>
<th>Null</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese</td>
<td>0.31 (0.35)</td>
<td>0.36 (0.36)</td>
<td>0.51 (0.37)</td>
<td>0.37 (0.38)</td>
<td>0.85 (0.41)*</td>
<td></td>
</tr>
<tr>
<td>Overweight†</td>
<td>0.09 (0.30)</td>
<td>0.12 (0.30)</td>
<td>0.08 (0.30)</td>
<td>0.01 (0.30)</td>
<td>0.19 (0.34)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity‡</td>
<td>-0.20 (0.33)</td>
<td>0.03 (0.33)</td>
<td>0.07 (0.34)</td>
<td>1.22 (0.53)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.09 (0.02)***</td>
<td>0.09 (0.02)***</td>
<td>0.09 (0.02)***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE ε4†</td>
<td>0.87 (0.27)***</td>
<td>0.95 (0.27)***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ObesexEthnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-2.11 (0.85)*</td>
<td></td>
</tr>
<tr>
<td>OverweightxEthnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.23 (0.72)</td>
<td></td>
</tr>
</tbody>
</table>

-2LL  551.07  550.70  525.49  515.12  508.75

Key: *p<0.05; **p<0.005; ***p<.0005
† Reference is Underweight or Normal
‡ Reference is Non-Hispanic
†† Reference is No APOE ε4 status
Table 4. Hazard Ratio Estimates Based on Model 4 Fit, UCSD Shiley-Marcos ADRC Longitudinal Study, 1985-2013 (N=339)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body Mass Index</strong></td>
<td></td>
<td></td>
<td>0.5456</td>
</tr>
<tr>
<td>Obese</td>
<td>1.45</td>
<td>0.69-3.03</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1.01</td>
<td>0.56-1.82</td>
<td></td>
</tr>
<tr>
<td>Underweight or Normal‡</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td>0.8441</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.07</td>
<td>0.56-2.07</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic‡</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.09</td>
<td>1.06-1.13</td>
<td></td>
</tr>
<tr>
<td><strong>APOE ε4 Presence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.39</td>
<td>1.42-4.02</td>
<td>0.0010</td>
</tr>
<tr>
<td>No‡</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

‡ Indicates reference category

Table 5. Hazard Ratio Estimates Based on Model 5 Fit, UCSD Shiley-Marcos ADRC Longitudinal Study, 1985-2013 (N=339)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.10</td>
<td>1.06-1.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APOE ε4 Presence†</td>
<td>2.59</td>
<td>1.53-4.39</td>
<td>0.0004</td>
</tr>
<tr>
<td>Hispanic x Obese‡</td>
<td>0.28</td>
<td>0.07-1.23</td>
<td>0.0127</td>
</tr>
<tr>
<td>Hispanic x Overweight‡</td>
<td>0.35</td>
<td>0.10-1.24</td>
<td>0.0871</td>
</tr>
<tr>
<td>Non-Hispanic x Obese‡</td>
<td>2.34</td>
<td>1.06-5.17</td>
<td>0.0127</td>
</tr>
<tr>
<td>Non-Hispanic x Overweight‡</td>
<td>1.21</td>
<td>0.62-2.34</td>
<td>0.0871</td>
</tr>
</tbody>
</table>

† Reference is No APOE ε4 status
‡ Reference is Hispanics with Underweight or Normal BMI
¶ Reference is Non-Hispanics with Underweight or Normal BMI

BMI category, ethnicity, age, and APOE ε4 presence were individually added to the model. After adjusting for BMI category, ethnicity, and APOE ε4 presence, age was significantly associated with incident MCI (p<0.0001, 95% CI 1.06-1.13). In fact, for every 1 year increase in age, the risk of developing MCI increased by a factor of 1.09, after adjusting for other variables in the model. In regards to APOE ε4 presence, those who had a copy of the APOE ε4 allele were 2.39 times more likely to develop MCI compared to those who did not have a copy (p=0.0010, 95% CI 1.42-4.02).
Additionally, the analysis examined the interaction between ethnicity and BMI to determine if there may be an underlying relationship to consider. Interestingly, the predictors BMI category and ethnicity were not individually significant until the interaction between the two was added to the model. Thus, the final model included BMI, ethnicity, age, APOE ε4 presence, and the interaction between BMI and ethnicity (overweight x Hispanic; obese x Hispanic, overweight x non-Hispanic, obese x non-Hispanic). The relationship between the BMI x ethnicity interaction and incident MCI is also displayed graphically in Figure 7.

![Survivor Functions for Reference Setting](image)

**Figure 7.** Kaplan-Meier survival curves that displays the fitted relationship between incident MCI and the BMI x ethnicity interaction, adjusting for age and APOE ε4 presence. Survival displayed as years post enrollment.

From the final model including this interaction term (Table 5), we can infer that the relationship between BMI and MCI risk varies according to whether an individual is Hispanic or non-Hispanic, after adjusting for age and APOE ε4 presence. Specifically, among non-Hispanics, those who were obese were 2.34 times more likely to develop MCI compared to those who fell into the normal or underweight BMI category ($p=0.0127$, 95% CI
1.06-5.17), after adjusting for age and APOE ε4 presence. Similarly among non-Hispanics, those who were overweight were 1.21 times more likely to develop MCI compared to those who were in the normal or underweight BMI category, after adjusting for age and APOE ε4 presence. However, this particular finding was only significant at the $p$-value of 0.10. Notably, an opposite effect was determined in Hispanics. Among Hispanics, those who fell within the underweight or normal BMI category were 3.57 times more likely to develop MCI compared to those who were obese ($p=0.0127$, 95% CI 0.81-14.29). In addition, Hispanics with a normal or underweight BMI were 2.86 times more likely to develop MCI compared to those who were overweight ($p=0.0127$, 95% CI 0.81-10.00). These results were also consistent with the survival curves displayed in Figure 7. As shown in the figure, obese or overweight Hispanics and underweight or normal BMI non-Hispanics had better survival (greater odds of not developing MCI). In contrast, underweight or normal BMI Hispanics and obese or overweight non-Hispanics had worse survival (greater odds of developing MCI). The predictors and covariates in the final model met the proportional hazards assumption that this analysis requires.
CHAPTER 5

DISCUSSION

KEY FINDINGS

The primary aim of this analysis was to investigate whether BMI could predict incident MCI among a recruited cohort of cognitively normal older adults. A growing body of literature has surrounded the topic of MCI, given that it is gaining recognition as a preclinical stage to AD. However, both limited and conflicting literature exists on modifiable risk factors for MCI, such as BMI. In the present study, baseline BMI category (underweight/normal, overweight, obese) was not found to be significantly associated with MCI risk, prior to and after adjusting for covariates (age and APOE ε4). Likewise, BMI used as a continuous measure did not produce significant results. These findings were not unexpected, given that BMI has not been consistently shown to be related to MCI nor AD (Alzheimer’s Disease International, 2014).

Ethnicity was also of particular interest in this analysis. Similar to BMI, ethnicity was not significantly related to MCI risk in neither the bivariate analysis nor the multivariable analysis prior to adding the interaction between BMI and ethnicity. Interestingly, the BMI x ethnicity interaction was statistically significant at the $p<0.05$ level. Further investigation into the relationships between the individual BMI levels and ethnicity categories revealed novel results. Results for the non-Hispanics were expected and consistent with current literature – obese non-Hispanics were at greater risk of developing MCI compared to non-Hispanics who fell into the underweight or normal BMI category. However, the opposite was true for Hispanics, which has not been previously described in literature – Hispanics who had an underweight or normal BMI were more likely to develop MCI compared to those who were obese. Similar results were found when comparing overweight Hispanics/non-Hispanics to Hispanics/non-Hispanics who had an underweight or normal BMI.
Among covariates included in the analysis, age and APOE ε4 presence were significantly associated with MCI risk. Every one year increase in baseline age resulted in a 10% increase in MCI risk, after adjusting for other predictors. This was not unexpected, given that older age has been widely recognized as a risk factor for AD, MCI, and other forms of cognitive impairment (Bennett et al., 2002; Tang et al., 1996; Thies & Bleiler, 2013). APOE ε4 presence has also been described to increase AD risk, however its relationship with MCI has been less clear (Perquin et al., 2012; Raber, Huang, & Ashford, 2004). In this analysis, APOE ε4 presence increased MCI risk by a factor of 2.59, after adjustment in the final model. This finding not only validates APOE ε4 as a potential risk factor for MCI, but it also indicates MCI as a potential preclinical stage to AD given that APOE ε4 is so contiguous with AD (Elias et al., 2014; Sperling et al., 2011).

**STRENGTHS AND LIMITATIONS**

Among the few studies that have assessed potential modifiable risk factors for MCI, this was the first attempt to specifically investigate BMI as the primary predictor of interest. Furthermore, the interaction between BMI and MCI had not been studied up to this point. Much of the research related to cognitive impairment and associated risk factors has focused on AD or other dementias. However, given that MCI may be the preclinical stage for AD or other dementias, it is crucial to study predictors of MCI specifically in hopes of delaying or preventing the onset of AD or other dementias through interventions that target these risk factors.

The greatest strength of this analysis was derived from the prospective nature of the ADRC Longitudinal study, which allowed for time-to-incident MCI analysis. This is much more valuable in identifying risk factors for MCI versus simply examining associations from a cross-sectional perspective. With this longitudinal design, BMI could therefore be studied as a potential predictor of MCI. Furthermore, a unique combination of characteristics, such as history of diabetes and APOE ε4 presence, were controlled for during the analysis, providing a model for future studies examining risk factors for MCI. The strengths of this analysis are also rooted in the study procedures conducted by the ADRC. During the enrollment process, participants were recruited through multiple outlets, including public advertising (e.g., radio ads), community health fairs, and local clinics. Thus, this resulted in community-based
cohort that was generally representative. Standardized data procedures and highly skilled and trained staff also add to the validity of the data. Participants undergo very thorough and comprehensive neuropsychometric assessments, and a panel of experts are involved in the diagnosis of each subject. Furthermore, of those who received an MCI diagnosis, individuals who specifically had the a-MCI were included in this analysis and those who had the na-MCI were excluded. Given that a-MCI is the MCI subtype that is most related to AD, this strengthens the justification behind studying MCI as a preclinical stage to AD.

Similar to other community-based cohort studies, the present study had several limitations. The sample size was relatively small, with 339 participants included. After selecting for characteristics of interest, the sample reduced by 24%. The smaller sample size also prevented assessment of the life-course of BMI. For example, midlife BMI could not be examined. All participants at all ages were required to obtain a sample that was fit for analysis. In addition, prior to established MCI criteria, “at risk for AD” was used as a proxy for MCI. This prevents confirmation of true MCI diagnoses prior to 2004. However, given that MCI is considered to be a preclinical stage to AD, it is likely that these were, in fact, MCI cases. Furthermore, the “at risk for AD” description is most associated with the a-MCI subtype, which helps maintain consistency in regards to the study outcome (given that the a-MCI subtype was what was included in this analysis). Finally, although the analysis did control for a variety of covariates, other important characteristics, such as hypertension and history of heart disease, were not included due to missing data.

**IMPLICATIONS AND FUTURE DIRECTIONS**

The overall goal in identifying risk factors for MCI, especially modifiable ones, is to then establish and implement interventions that will potentially delay or prevent the progression to AD. Although MCI has gained increasing attention in the aging and dementia field, limited research exists on risk factors specific to MCI. This analysis found APOE ε4 presence and older age to significantly increase MCI risk, however additional research is needed to validate these findings. Furthermore, this study highlights the importance of studying interactions between risk factors – for example, the effect that an unmodifiable risk factor (e.g., ethnicity) may have on a modifiable one (e.g., BMI) and vice versa.
The novel findings from the assessment of the interaction between BMI and ethnicity bring up several questions. Studies have shown that although a greater number of non-Hispanics have AD, Hispanics are at a greater of risk of developing AD (Fitten et al., 2001; Rose, 2005; Tang, 1998; Thies & Bleiler, 2013; Unverzagt et al., 2001). This may suggest that a similar relationship with MCI exists among those ethnic groups. Higher rates of overweight and obesity as well as other conditions (i.e., diabetes, cardiovascular disease) have been described as possible explanations for this disparity (Fitten et al., 2001; Rose, 2005; Tang, 1998; Thies & Bleiler, 2013; Unverzagt et al., 2001). However in the present study, Hispanics who were obese or overweight were at a lower risk of developing MCI compared to their underweight or normal BMI counterparts. One proposed explanation for this was that APOE $\varepsilon4$ was less present among the obese and overweight Hispanics and/or Hispanics overall in the sample. This would have been plausible, given that studies have shown that a smaller proportion of Hispanics have a copy of the APOE $\varepsilon4$ allele compared to non-Hispanics (Campos, Edland, & Peavy, 2013; Maestre et al., 1995; Mayeux et al., 1993). However, additional analyses indicated that percentages of APOE $\varepsilon4$ were generally consistent among all levels of BMI and ethnicity categories. In addition, age was examined for its potential effect, given that both MCI and AD risk increases with age (Cherbuin et al., 2009; Ganguli et al., 2000). Similar to APOE $\varepsilon4$ presence, results showed that there were no significant differences in age among the ethnic categories or levels of BMI.

Although studies have shown that BMI is significantly related to AD risk independently of other comorbidities, it is possible that these moderators are affecting the relationship between BMI, ethnicity, and MCI risk (Buchman et al., 2005; Profenno et al., 2010; Whitmer et al., 2007). Furthermore, there may be factors indirectly driving the relationship. For example, stress and depression may be underlying factors, which have been shown to increase AD risk (Cherbuin et al., 2009; Sosa-Ortiz et al., 2012). Obesity has been described as a risk factor for depression in individuals (Luppino et al., 2010). However, being obese or overweight is generally more accepted among Hispanics vs. non-Hispanics (Hicken et al., 2013; Seo & Torabi, 2006). Thus, it is possible that a higher proportion of obese or overweight non-Hispanics in the study sample have experienced stress or depression compared to the overweight or obese Hispanics, and it is this that is driving the increased
MCI risk. Further investigation into this BMI-ethnicity relationship is necessary in order to better understand how BMI affects MCI or AD risk.
REFERENCES


