THE RELATIONSHIP OF BODY MASS INDEX WITH BEHAVIOR, BRAIN STRUCTURE AND LONGITUDINAL CHANGES IN MILD COGNITIVE IMPAIRMENT

By

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ABSTRACT

THE RELATIONSHIP OF BODY MASS INDEX WITH BEHAVIOR, BRAIN STRUCTURE AND LONGITUDINAL CHANGES IN MILD COGNITIVE IMPAIRMENT

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Mild Cognitive Impairment (MCI) is a syndrome characterized by cognitive deficits that lie on the spectrum between normal aging and dementia. The clinical course of MCI at diagnosis is not easily predictable, because it represents a heterogeneous population. Neuropsychiatric symptoms (NPS) and midlife obesity increase the likelihood of developing Alzheimer's disease; yet, these two risk factors have not been studied together in MCI. The goal of this dissertation is to examine the relationships of weight measured by body mass index (BMI), with behavior, brain structure, and longitudinal changes in MCI. First, we examined the relationship of obesity and NPS in MCI. It is unknown whether obesity or related health conditions modify the risk of NPS or severity of cognitive impairment in MCI. We found that in MCI, obese subjects were younger and had a higher frequency and severity of affective (depression and anxiety) symptoms near the time of diagnosis. In addition, we examined a number of obesity-related disorders to determine if the relationship between BMI and NPS was more strongly mediated by these secondary factors than BMI itself. We found that type-2-diabetes mellitus (T2DM) and obstructive sleep apnea, also exhibited a specific frequency and severity of NPS. While there were no effects of obesity on cognition, T2D subjects had lower cognitive scores and nearly double the NPS burden. Next, we wanted to determine whether BMI had an effect on brain structure. We selected 36 regional brain volumes related to MCI or weight from the Alzheimer's disease Neuroimaging Initiative (ADNI) dataset. The ADNI sample provided over 600 MCI subjects and we found a main effect of BMI on brain volume in 14 out of 36 regions. Surprisingly, normal weight subjects had lower

brain volumes. Since normal weight subjects were significantly older we separated the sample by middle age (55-65 years) and Seniors (>65 years) to determine if age group mediated the effects on brain structure and found that Seniors had lower brain volumes and there was no difference in brain structure for middle-aged subjects. Finally, we measured the relationship of BMI on longitudinal behavioral and cognitive changes over two years and measured the survival distributions of BMI, age, and NPS groups. Over two years NW subjects had greater cognitive deficits. Senior subjects with low baseline NPS showed a faster progression to Alzheimer's dementia. These findings indicate that in MCI obese subjects may have a higher likelihood of NPS and those that have T2D may be at risk for cognitive impairment. In addition, NW MCI subjects may be at an increased risk for brain atrophy and lower cognitive scores. This research may inform lifestyle interventions in regards to obesity, and clinical treatment for NPS prior to the establishment of irreversible cognitive impairments. Further, low body weight should be monitored in old age for progressive gray matter atrophy and cognitive decline.

For my grandmother Cornelia (Cooka) Hannah,
who showed me that “He’s able” in life and in death.

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KEY TO ABBREVIATIONS

MCI	Mild Cognitive Impairment
AD	Alzheimer's Disease
BMI	Body Mass Index
NPS	Neuropsychiatric Symptoms
NPI-Q	Neuropsychiatric Inventory Questionnaire
GDS	Geriatric Depression Scale
NW	Normal Weight
OW	Over-Weight
OB	Obese
T2D	Type-2-Diabetes
OSA	Obstructive Sleep Apnea
MSU	Michigan State University
COGENT	Cognitive and Geriatric Neurology Team
ADNI	Alzheimer's Disease Neuroimaging Initiative
MRI	Magnetic Resonance Imaging
DTI	Diffusion Tensor Imaging
JHU	John's Hopkins University
FSL	FMRIB's Software Library
TBSS	Tract Based Spatial Statistics
DMN	Default Mode Network
CCN	Cognitive Control Network
U.S.	United States

MMSE	Mini Mental Status Examination
ADAS-cog 13	Alzheimer's Disease Assessment Scale – Cognitive 13
CDR	Clinical Dementia Rating Scale
ANOVA	Analysis of Variance
MANOVA	Multivariate Analysis of Variance
SD	Standard deviation
SE	Standard error

INTRODUCTION

Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is a syndrome characterized by cognitive deficits that lie on the spectrum between normal aging and dementia. The clinical course of MCI at diagnosis is not easily predictable, because as a whole, MCI represents a heterogeneous population. However, MCI is associated with an increased likelihood of developing Alzheimer's disease (AD), with an average conversion rate to dementia of 10-15% per annum over five years. There is an increased risk of AD for amnestic (memory-impaired) MCI subtypes [1–4]. The high risk of developing AD makes the study of MCI a priority for better understanding prodromal states of dementia. This is largely based on the theory that early cognitive deficits are the result of an underlying neuropathology.

The diagnostic criterion for MCI were originally established by Ron Petersen and colleagues in 1999[1]. A few years later these criteria were revised to capture the heterogeneity in the cognitive deficits presented. MCI is defined by the following criteria; (a) the subject does not have normal cognition and is not demented (b) cognitive deterioration is evident as reported by the subject and an informant or objectively measured over time (c) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired[5]. Potential outcomes of MCI over time include; (a) stable MCI, never progressing to AD or other forms of dementia (b) AD; (c) other dementias (i.e. Frontotemporal dementia (FTD), vascular dementia (VaD), Lewy body dementia (LBD)); and lastly, in some cases, (d) reversion to normal cognition.

Due to the heterogeneity of MCI, identifying factors within this population that increase the risk for dementia are essential. These factors or biomarkers, measured characteristics that are indicative of an underlying biological state, condition or disease process, are an important area of

dementia research. Biological, behavioral and neuroimaging biomarkers of an underlying AD pathology have been previously reported in MCI and include decreased cortical thickness and volume of the hippocampus and medial temporal lobe[6], hypometabolism of the posterior cingulate cortex (PCC)[7], amyloid beta deposition[8,9], Apolipoprotein e4 allele status[10,11] and depression.

All individuals who develop AD pass through the transient state of MCI and express varying degrees of behavioral, cognitive and brain structure changes. Clinical symptoms include mild impaired function in daily activities, behavior and mood. In addition to these factors epidemiological studies have indicated that age, being female and decreased educational attainment increase the risk for the development of AD and conversion from MCI[12,13] . It is now known that the changes that occur in the transition from normal cognition to AD begin decades prior to clinical symptoms of dementia[14,15].

Cognitive subtypes are the only recognized subgroups of MCI. In MCI, subtypes that have prominent memory deficits, amnestic MCI (aMCI) are at an increased risk for dementia[16,17], compared to non-amnestic MCI and multi-domain MCI subtypes. However, patients from all subtypes of MCI can convert to AD despite their initial cognitive impairments. Many research studies and clinical trials focus predominantly on amnestic MCI patients in order to study early stages of AD, yet non-cognitive factors that are highly prevalent in MCI are beginning to gain more attention. Non-cognitive risk factors such as behavioral changes and metabolic disorders may provide additional understanding of the underlying pathology of MCI and allow for the construct of a profile of specific subgroups that may be at an increased risk for AD.

Neuroimaging in Mild Cognitive Impairment

Neuroimaging has been an important tool in understanding the pathophysiology of MCI and AD[18–22]. AD is considered to be a disease of the limbic system[23,24]. Primary regions altered due to AD include the cingulate gyrus, hippocampus, parahippocampal gyrus (PHG), entorhinal cortex and fornix. Changes within these regions have been quantified using various neuroimaging techniques to gauge structural and functional deficits. Structural neuroimaging techniques include volumetric MRI (vMRI) which assess the integrity of grey matter regions, and diffusion tensor imaging (DTI) which allows for the estimation of microstructural white matter fiber tract integrity[18,21,25]. Brain atrophy in limbic regions, the bilateral hippocampus, amygdala, fornix, and parahippocampal gyri on vMRI have been correlated with cognitive deficits of MCI subjects[25,26]. Most prominently, volumetric measures of the hippocampus correlate with decreased Mini Mental Status Exam (MMSE)[27] scores and positively predict conversion to AD[28]. In addition, diffusion imaging has allowed for better understanding of the structural changes of white matter tracts and neuronal health. The disease process of AD and MCI encompass significant white matter changes including decreased volume, lesions and hyperintensities in fornix, cingulum and frontal white matter[24,29–31].

Functional imaging techniques include measures of cerebral glucose metabolism, task dependent activation of brain regions and functional connectivity of brain networks at rest, through the use of flourodeoxyglucose – Positron Emission Tomography (fdg-PET), stimulation-based functional MRI (fMRI) and resting state fMRI (rsfMRI) respectively. A reduction in glucose metabolism in the posterior cingulate cortex (PCC) is a reliable early clinical biomarker for AD pathology in MCI[32,33]. Many studies have analyzed the reductions in task-dependent activation in brain regions affected by AD in memory retrieval, attention, and executive

processing tasks [34–36]. Neurodegenerative diseases such as AD also have altered functional connectivity of the brain at rest, with reductions of region and network based connectivity among temporal, parietal and frontal regions compared to healthy controls[37,38]. However, in some regions increased connectivity is seen and speculated to be a compensation for loss of function in regions affected by AD pathology. Resting state fMRI measures blood oxygen level dependent (BOLD) signal fluctuations of the brain at rest [36].

In theory, regions that are functionally connected exhibit similar or correlated activity at rest. The most widely researched resting state network is the Default Mode Network (DMN) [39]. Brain activity related to internal thoughts such as autobiographical memory and thinking of the future utilize DMN brain regions. The DMN shows increased activity at rest, is deactivated during tasks, and is anchored in the posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) with prominent brain nodes of connectivity in the medial temporal lobe (MTL) and angular gyrus. The network connectivity of the DMN is altered in normal aging and illness, including MCI[19,40,41]. Discovery of the DMN has launched the search for other resting state networks involved in numerous cognitive and behavioral disorders[42]. Among these is the cognitive control network (CCN)[43]. The CCN is involved in attention, working memory, and self – control. The CCN has major nodes within the dorsal anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC), and portions of the parietal lobe. In functional imaging studies the DMN is deactivated in the presence of a task where the CCN is active in related tasks making them anti-correlated networks[37]. Network and seed based analysis of CCN regions correlate with the degree of executive dysfunction, more prominent in naMCI[21].

Neuropsychiatric symptoms in Mild Cognitive Impairment

Research studies indicate that individuals with MCI have an increased prevalence of

neuropsychiatric symptoms (NPS) compared to the normal population[44–46]. Apathy, depression and anxiety are the most prevalent NPS in MCI[4,44,47,48]. In cognitively normal older adults, NPS such as depression and apathy correlate with cognitive decline and the development of MCI at a higher rate than cognitively normal subjects without NPS[25,49,50]. In MCI, apathy symptoms are correlated with conversion to AD by almost 7 times, the presence of multiple symptoms on the neuropsychiatric inventory-questionnaire (NPI-Q) have an additive effect on progression to AD[4]. There is also evidence that NPS in general may be a marker of MCI severity, decreasing the time to progression to dementia by almost 2.5 times[44,51]. Neuropsychiatric symptoms in MCI measured by the NPI-Q with cut off scores of 0-3 and ≥4 are a reliable indicator of group differences; scores ≥4 are more likely to be aMCI with increased medical comorbidities and functional impairments[52]. As cognitive scores decline over time, NPS and functional impairments increase from MCI to AD and appear to be a result of brain damage. Further, the most frequently reported NPS in AD also overlap with those in MCI including, apathy and depression for both disorders[50,53,54]. There may be a link in the transition to dementia between cognitive decline and NPS prevalence and severity. Thus, behavioral symptoms lie on the continuum of AD pathology, making their presence in early cognitive impairments a feature of important research investigation. Proper identification of NPS syndromes in MCI may aid in discerning the etiology of MCI subtypes, and provide a more reliable prognosis at the time of diagnosis.

Neuroimaging of neuropsychiatric symptoms

Neuroimaging has aided in the quantification of brain changes in the presence of psychiatric symptoms for many years. Many studies have sought to identify specific brain regions and neural networks important in emotional regulation. Brain imaging of depression with

and without MCI has been widely researched and has provided evidence for structural changes in grey and white matter related to affect. For example, white matter microstructural changes in depression include decreased fractional anisotropy (FA) in white matter sub-adjacent to the ACC, superior frontal gyri, left middle frontal gyrus[55,56]. In a direct investigation of NPS in MCI, low FA values in the anterior cingulate were most related to NPI-Q symptoms of irritability, agitation, depression, apathy and nighttime behaviors. Another study using DTI in anxiety disorders found decreased FA values of the uncinate fasciculus (UF) and the inferior longitudinal fasciculus[57]. The UF tract connects the amygdala and orbitofrontal cortex, important affective brain regions that demonstrate disrupted brain connectivity in the presence of NPS[26,58]. In addition cortical brain atrophy of subjects with high NPS is seen in the ACC, orbitofrontal and dorsal parietal lobe regions[20]. Psychopathology also attenuates the functional connectivity (FC) of the brain. Interestingly, FC in depressed patients increases within the thalamus and subgenual cingulate[59]. An example of this has been demonstrated in AD where, Balthazaar and colleagues found increased FC in mild AD patients between the ACC and anterior insula[54], which was related to NPS symptoms of hyperactivity (agitation, irritability, aberrant motor behavior, euphoria and disinhibition)[60].

Obesity and cognitive deficits

Obesity is a prevalent health condition in the United States affecting 36.5% of adults and 17% of youth (ages 2 – 19)[61] and is becoming more prevalent worldwide. Obesity is disorder characterized by excess body fat and low energy expenditure that is associated with an increased risk for health problems. The prevalence of obesity in the US has dramatically increased over the last 30 years and is highest among middle age (aged 40-65) and older adults (aged 66 and older). Obesity often occurs co-morbidly with conditions such as, Type 2 Diabetes, vascular diseases,

heart disease and sleep apnea, and it is the leading cause of work disability[62]. Additional side effects include decreased global brain volume, a high risk for the metabolic syndrome, a high likelihood of comorbid NPS and premature death[63]. Obesity is considered a modifiable health condition with the cause related to a combination of excessive food intact, lack of physical activity and genetic susceptibility[64]. A common measure of obesity is body mass index (BMI), which calculates body fat by taking into account a person's weight divided by the square of their height. There are 3 BMI groups, normal weight, overweight and obese. Body mass index is not as accurate as measure of waist to hip ratio or detailed body fat assessments[65], but it is widely used in research studies on obesity as it allows for a quick assessment of body fat using standard clinical measures of height and weight.

Multiple lines of evidence indicate a link between obesity and the development of neurodegenerative diseases[66–70]. Most importantly, obesity in midlife is associated with an increased likelihood of developing AD [54,67]. Obesity is association with changes to the central nervous system, including changes in appetite-regulating hormones, cortical and subcortical brain volumes reductions and increased deficits across age groups[71,72]. These may be a mediating factor in the development of cognitive impairments and eventually dementia as a result. Altered hormone signaling of leptin and ghrelin acting on the hypothalamus often occur in obesity[73,74]. Further, studies have shown decreased total brain volume and altered processing within brain regions involved in cognitive control, such as the CCN. Most studies examining the relationship between obesity and cognition have examined brain differences within weight groups of healthy middle aged and older adults or are retrospective studies that link obesity in middle age with an ultimate conversion to dementia later in life. However, few studies have investigated obesity within the transitional cognitive state of MCI.

Neuroimaging of obesity

There is evidence that chronic obesity affects the structure and function of the brain. Brain regions associated with obesity include those within networks of cognitive control. This association is hypothesized to be a cause of overeating due to a lack of inhibition which ultimately leads to obesity[75–77]. Primary brain regions of the CCN include the dlPFC, anterior cingulate cortex, orbitofrontal cortex, amygdala, hippocampus and nucleus accumbens[78,79]. Obesity in elderly adults is associated with decreased total grey matter volume[80]. In neuroimaging studies on obesity across age groups obese adults have lower brain volumes in many AD related regions, such as the temporal lobe, hippocampus, cingulate cortex, dorsolateral prefrontal cortex and posterior parietal cortex[75,81]. Thus, the correlation of brain volume decline and obesity may be a sensitive measure in those that develop a cognitive impairment. For example, adults obese in midlife exhibit significantly decreased brain volume in predominantly frontal and temporal lobes and in measures of global atrophy as they age[80,81]. Further, a study measuring the cortical thickness of regions in the CCN showed that between obese, non-obese and successful weight losers (maintenance of significant weight loss for a minimum 3 years), obese subjects had significant cortical thinning in the following regions: anterior insula, ventral striatum, rostral ACC and ventromedial PFC. In cognitively normal older adults, obesity has also been shown to decrease grey matter volume within the orbitofrontal cortex, anterior cingulate gyrus, hippocampus and basal ganglia. These results remained even after controlling for diabetes status, hypertension, and white matter hyperintensities[80]. To date, only one article has discussed the effect of obesity on brain structure specifically within MCI subjects. Ho et. al. examined the effects of obesity on brain volume in MCI and early AD subjects and found that BMI was

directly correlated with increased brain atrophy in frontal, temporal and parietal regions. Further, every point increase in BMI was associated with a 0.5% - 1.5% decrease in brain volume[82].

Diffusion tensor imaging of white matter structural integrity depict difference in white matter tracts between normal weight and obese individuals. Most prominently, measures of decreased FA of the fornix and corpus callosum in obese subjects has been seen in multiple studies[83–85]. In addition a recent study using DTI showed white matter atrophy and decreased FA values among obese subjects within the inferior frontal gyrus, temporal gyri, insular cortex, occipital gyri and amygdala[85]. Overall there was a negative relationship between body fat and WM volume.

Literature on the functional connectivity (FC) of the obese brain in adults is limited and currently has not been investigated in MCI. However in adolescents, fMRI studies have shown activation of the insula and portions of the operculum in regard to the anticipation of food[77]. In a similar procedure in young adults, food anticipation (cravings) resulted in increased brain activation in the hippocampus, insula and caudate[86].

Comorbidity of obesity and neuropsychiatric symptoms

Despite the difference in factors that contribute to the onset of obesity or NPS independently, they often occur as comorbid conditions across age groups[87]. Compared to normal weight adults, obese subjects are more likely to exhibit symptoms of depression, apathy and anxiety. Adults with severe psychiatric disorders exhibit a prevalence of obesity of approximately 50 percent, compared to the national average of 30%[88]. Further, obesity and NPS can be predictive of one another. For example, with depression are more likely to be obese as adults[89] and obese adolescents are more like to develop psychiatric symptoms comorbid with obesity in adulthood[90]. A five-year longitudinal study of adults 50 and older measured the

relationship between obesity and depression and found that obese subjects were twice as likely to be depressed at the end of 5 years and the depressed patients at baseline were more likely to be obese after 5 years[91]. However, depression did not predict obesity at follow up. The relationship between NPS and obesity in the literature is unclear and it is unknown how they interact in MCI.

The proposed neurocircuitry of both NPS and obese involve dominant pathways from the prefrontal cortex with relays through the cingulate gyrus[79,92–94], yet the interactive effects of obesity and NPS on brain volumes have rarely been studied, especially in older adults, and not at all in MCI. In MCI, NPS and obesity have different times of onset and possible course of pathology: where as obesity is likely to cause changes in brain structure, NPS may be a symptom of such changes. A link between obesity and NPS has been hypothesized as low-grade inflammation[95]. Chronic inflammation is believed to lead to neurodegeneration by affecting the expression of amyloid-beta precursor protein[96]. While both obesity and NPS increase the risk of AD they have not been studied together in MCI. This dissertation will investigate the relationship of obesity, measured by body mass index, and NPS across clinical, neuroimaging and longitudinal measures in MCI subjects.

Summary

Since the original description of MCI in 1999, research in the field has focused on longitudinal follow-up of MCI samples, and refining the psychometric and eligibility criteria for MCI and its subtypes in order to maximize predictive sensitivity and specificity for the disorder over time. Despite the heterogeneity of MCI, subtypes (aMCI/naMCI) are based solely on cognitive criteria. The majority of research investigates aMCI/naMCI-related cognitive changes of MCI and their relationship to disease progression, neuroimaging markers and behavior, but this only captures a piece of the puzzle. Obesity affects the central nervous system and is also

associated with cognitive and behavioral changes. Despite the high prevalence of obesity across age groups this factor is relatively absent from the body of work that seeks to characterize and provide an understanding for MCI and relationships between the brain and behavior. This problem is exacerbated by the fact that there is no cure or effective treatment for either MCI or AD. The most popular and widely distributed drug for AD, Aricept (donepezil) produces small improvements in the cognitive symptoms of AD, and is relatively ineffective in MCI[97,98]. Identifying non-cognitive markers or risk factors for AD may provide clinicians with an avenue for concentrated interventions for particularly high-risk individuals within the larger MCI population.

Thus, the goal of this dissertation is to bring together non-cognitive modifiable risk factors for AD that may further characterize behavioral, brain, and longitudinal changes in MCI. This research may inform lifestyle interventions in regards to obesity, and clinical treatment for NPS prior to the establishment of irreversible cognitive impairments. Prior to this collection of research, obesity and NPS have not been studied together in MCI. There is a lack of knowledge regarding the comorbidity of obesity and NPS in MCI, the interaction of obesity and NPS on brain structure and white matter integrity, and disease progression related to these factors. This dissertation will address these gaps in knowledge by using body mass index as a measure of adiposity in MCI subjects. The following research aims will,: 1) identify the prevalence of obesity in MCI and its comorbidity with NPS; 2) assess volumetric and white matter brain changes related to obesity; and 3) examine longitudinal changes in cognitive, functional and behavioral measures and progression from MCI to AD.

CHAPTER 1

OBESITY AND CO-MORBID CONDITIONS ARE ASSOCIATED WITH SPECIFIC NEUROPSYCHIATRIC SYMPTOMS IN MILD COGNITIVE IMPAIRMENT

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Introduction

Behavioral changes or neuropsychiatric symptoms are prevalent in Mild Cognitive Impairment (MCI) and are associated with an increased likelihood of conversion to dementia[99]. MCI is a transitional state between normal cognition and dementia and the presence of neuropsychiatric symptoms (NPS) predict the progression of MCI to AD, decreasing the time of progression to dementia by 2.5 fold [4,50]. Neuropsychiatric symptoms such as depression, anxiety and apathy are a hallmark of Alzheimer's disease (AD) [48,100]. As high as 80% of AD patients have at least one symptom on the Neuropsychiatric inventory with affective and apathy symptoms having the highest prevalence[53,101]. In MCI, depression is one of the most prevalent symptoms and has been directly related to cognitive decline and the development of dementia[102,103].

Obesity is a common disorder characterized by excess adipose tissue and is associated with cognitive deficits and an increased likelihood of developing dementia when present at midlife[104]. The prevalence of obesity in the U.S. has nearly tripled over the last 30 years and is highest among middle age and older adults [105]. Side effects of chronic obesity include lower global brain volume, a high risk for metabolic syndrome, and premature death [63]. Further, obesity affects cognition [66] and often occurs co-morbidly with NPS across age groups [87]. Additional conditions, consequences of obesity such as type 2 diabetes, sleep apnea and other vascular disorders are also associated with cognitive decline and increased neuropsychiatric symptoms. Multiple lines of evidence demonstrate a link between midlife obesity and the development of dementia [66–68]. However, the relationship between NPS and obese subjects and cognitive decline within early MCI has not been studied.

Neuropsychiatric symptoms and obesity have not been measured together to determine their co-morbidity in MCI and interactions with cognition. In the present study, our hypothesis is

that in MCI, obesity is associated with higher total NPS scores and a higher prevalence and severity of affective symptoms (depression and anxiety), as well as more extensive cognitive loss as measured by MCI severity compared to normal weight subjects. We sought to first identify the prevalence of obesity, obesity-related health conditions, and NPS within MCI, examining their relationship and their effect on the severity of cognitive impairment. We then clustered similar NPS together, and examined the frequency and severity of behavioral clusters across weight groups and BMI-related health conditions.

Methods

All study data came from medical records dating between 2004 and 2014 from a tertiary geriatric neurology clinic at Michigan State University serving the mid-Michigan area. Clinical and behavioral data were taken at the time of diagnosis of MCI. This study involved minimal risk to human subjects and a waiver of consent was requested and approved by the Michigan State University Institutional Review Board.

MCI diagnosis

The diagnosis of MCI was determined according to Petersen's Criteria [1] by an expert neurologist (A. Bozoki). The diagnostic process included an initial clinical evaluation by the neurologist followed by a neuropsychological assessment battery, MRI (head CT if MRI was contraindicated) and serologic testing for metabolic profile, thyroid function and vitamin B12 level. The neuropsychological assessment battery (a modified CERAD battery [106], described in further detail in the MCI Severity section), assessed memory, verbal and visual delayed recall, language, visuospatial and executive functions, and was administered to all subjects. Subjects scoring $\geq$ -1.5 standard deviations (SD) below the education and age-adjusted mean in one or more cognitive domains were classified as MCI. The MCI sample represented a heterogeneous population consisting of amnestic MCI, non-amnestic MCI and multi-domain MCI subtypes.

Inclusion criteria for this study were as follows: subjects were between the ages of 50-95 years, able to speak, comprehend and read English with at least 8 years of education, and a Mini Mental Status Examination (MMSE) [27] score between 24 - 30. Subjects were excluded if they had a history of a coexisting central nervous system disorder or uncontrolled depression that could account for the cognitive impairment, any uncontrolled or unstable medical condition, and alcohol or substance abuse within the last two years. Exclusion criteria were determined based on medical records review. Over the 10-year period, there were 667 subjects with neuropsychometric data. Of the 667 subjects examined, 117 were diagnosed with MCI. A total of 4 subjects were excluded from the study due to a history of major depression (n = 3) and stroke (n = 1). Our final sample consisted of 113 subjects that met the inclusion criteria.

BMI groups

The MCI sample was grouped by traditional BMI criteria: normal weight (NW; BMI 18.5- 24.9), overweight (OW; BMI 25 - 29.9) or obese (OB; BMI $\geq$ 30). Height (in inches) and weight (in pounds) measurements were taken at the time of clinical diagnosis of MCI. BMI was converted to the unit kg/m^2 using the follow calculation, [(Weight (lb.) / Height^2 (in.)) x 703].

BMI-related disorders

A clinical history of BMI-related disorders was recorded in order to account for conditions that may be comorbid with increased weight [96] but pose an independent risk factor for cognitive decline [107], or have an increased prevalence of neuropsychiatric symptoms [108]. These included, type 2 diabetes (T2D), hypertension (HTN), hyperlipidemia (HL), gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA). The presence or absence of each of these conditions was recorded for each subject at the time of MCI diagnosis. In addition, blood pressure recordings at the time of diagnosis were used to calculate a mean arterial pressure (MAP) value for each subject as a measure of cardiovascular health.

Neuropsychiatric symptoms

Neuropsychiatric symptom were measured using the Neuropsychiatric Inventory Questionnaire (NPI-Q) [109] and the Geriatric Depression Scale –short form (GDS) [110]. The NPI-Q is a validated measure for assessing behavioral disturbances across 12 different domains in a brief caregiver-reported questionnaire [109]. These include; delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, sleep and nighttime behavioral changes, and appetite and eating disorders. An informant familiar with the subject reported NPI-Q symptoms, by rating each symptom first for their presence (yes / no), and then severity (range of 1 - 3) with a total of 36 possible points. Behavioral changes reported on the NPI-Q reflect symptoms present within one month of testing. The self-reported 15-point GDS scale was used for further quantification of depressive symptoms. Mild NPS was designated as a total score ≥ 1 and moderate NPS as ≥ 4 for each test. Quantification of NPS burden was measured based on the total symptom score for each test and the prevalence of mild and moderate symptoms groups.

NPI-Q clusters

Neuropsychiatric Inventory- Questionnaire symptoms were grouped into clusters based on a prior research study demonstrating that specific neuropsychiatric inventory (NPI; original full test version) symptoms tend to cluster together in their prevalence and severity when they emerge as part of a dementia [60]. The benefits of assessing NPI/NPI-Q clusters instead of individual symptoms include both examination of underlying similarities in prevalence, progression of symptoms and biological correlates[111]. Thus, in the present study the 12 NPI-Q symptoms were grouped into 4 clusters: Hyperactivity (agitation, disinhibition, irritability, motor disturbances and euphoria), Psychosis (delusions, hallucinations, night-time behaviors), Apathy (apathy, appetite), and Affective (depression, anxiety). The presence of a symptom cluster

required the presence of at least one symptom within each cluster. The cluster severity was the average of the total score (0-3) across each symptom within a cluster for each subject.

MCI severity

To determine whether BMI groups were associated with an increase in MCI severity (MCI-SV), a z-score was computed for each cognitive test in the neuropsychological test battery, then averaged to obtain a mean overall z score for each subject. Included test measures evaluated global cognition (MMSE; Modified Mini Mental Exam (3ME) [112]), memory (CERAD Word List, immediate/delayed/recognition [113]), language (CERAD 15-item Boston Naming Test [114]; categorical and phonemic verbal fluency [115]), executive function (Trail Making Test [116]; Stroop [117]), and visuospatial tests (CERAD Constructional Praxis, immediate/delayed [118]).

Statistical analysis

The analysis of variance (ANOVA) model was used to compare NPI-Q total score, GDS score, NPI-Q cluster severity and MCI severity scores across BMI groups. These comparisons were further adjusted for age and education using the analysis of covariance (ANCOVA) model. Specific BMI-related disorders that had a high prevalence of obesity were also used as independent variables. A chi-square test of independence was conducted to compare the frequency of NPI-Q clusters across BMI groups and BMI-related disorders. A Fisher's exact test was used to compare frequencies of NPI-Q clusters between groups when cell sample sizes were small. A direct examination of NPI-Q score differences between NW and OB were measured using a Student's t-test. And the relationship of BMI as a continuous variable with NPI-Q was measured using a Pearson's correlation. Statistical analysis was conducted using SPSS software (Hewlett Packard; Palo Alto, CA). A two-sided p-value less than 5% ($p<0.05$) was used for statistical significance.

Results

Demographics

A description of the study sample is reported in Table 1.1. Of the 113 MCI subjects included in the study, 110 had available BMI data and roughly 1/3 each were NW, OW and OB. Overall, the average BMI, mean age and MMSE of the sample was 27.4 kg/m^2, 74.1 years and 26.5 respectively. Over 90% of the sample was Caucasian with an average educational attainment of 14.6 years. Surprisingly, NW subjects were significantly older than OW and OB ($p < 0.001$). Overall, 78.6 % of subjects had at least one symptom on the NPI-Q and 87.3% had one symptom on the GDS. BMI was positively correlated with NPI-Q score (Pearson's $r = 0.225$; $p = 0.04$), and a direct comparison of NW and OB groups revealed a significantly higher prevalence of NPI-Q symptoms (Student's $t = 2.05$; $p = 0.045$, unadjusted). However, there was not an effect of BMI on NPS or cognitive measures in the ANOVA model.

TABLE 1.1. Demographic, cognitive and behavioral measures of the MCI sample grouped by BMI

Characteristic	Entire Group N = 113	NW N = 38	OW N = 39	OB N = 33	Statistic X^2 or F	P value
Age (yrs.)	74.3 (0.72)	78.74 (1.00)	72.4 (1.33)	71.2 (1.12)	11.97	<0.01[b,c]
Female, n (%)	53 (47)	20 (53)	20 (51)	11 (33)	3.23	0.20
Education (yrs.)	14.6 (0.31)	15.6 (0.49)	14.2 (0.49)	13.8 (0.64)	2.86	0.06
MMSE	26.5 (0.17)	26.0 (0.24)	26.8 (0.29)	26.7 (0.33)	2.24	0.11
MCI-Severity [a]	-0.89(0.06)	-1.04 (0.09)	-0.80 (0.09)	-0.82 (0.14)	1.78	0.18
NPI-Q score [a]	5.2 (0.56)	4.0 (0.72)	5.4 (1.02)	6.7 (1.27)	0.47	0.63
≥ 1, n (%)	68 (79)	25 (74)	26 (87)	17 (77)	1.72	0.42
≥ 4, n (%)	41 (48)	14 (41)	13 (43)	14 (64)	3.05	0.22
GDS score [a]	3.0 (0.26)	3.0 (0.35)	2.7 (0.35)	3.3 (0.73)	0.63	0.53
≥ 1, n (%)	91 (88)	34 (90)	33 (92)	22 (79)	2.70	0.26
≥ 4, n (%)	32 (31)	14 (37)	9 (25)	8 (29)	1.29	0.53

Abbreviations: MCI, Mild Cognitive Impairment; BMI, body mass index; MCI SV, MCI severity; MMSE, Mini-Mental State Examination; MCI-SV, MCI severity; GDS, Geriatric Depression Scale; NPI-Q, Neuropsychiatric Inventory Questionnaire; NW, normal weight; OW, overweight; OB, obese.

NOTE. Values are presented as mean (standard error) for continuous variables and n (%) for categorical variables. The statistic is chi-square test of independence for categorical variables (2 degrees of freedom) and an ANOVA F statistic for continuous variables. Significance was set as $p < 0.05$.Available behavioral data were as follows: NPI-Q, n = 86 and GDS, n = 102. Subscript a indicates adjustment for covariates age and education; b, indicates significant difference between NW and OB, c indicates significant difference between NW and OW.

BMI-related disorders

The frequency of all examined BMI-related disorders are displayed in **Table 1.2**. There was no difference in HTN, HL, GERD and MAP across BMI groups. However, a significantly higher proportion of T2D and OSA subjects were OB compared to NW and OW. Thus, T2D and OSA were used as independent variables in further analysis of individual NPI-Q cluster frequency and severity.

TABLE 1.2. The frequency of BMI-related disorders within BMI groups

BMI-related disorder	Entire Group	NW	OW	OB	X^2 or F	P value
GERD	14%	16%	13%	27%	0.24	0.89
HP	43%	34%	44%	52%	2.18	0.34
HTN	53%	53%	49%	58%	0.56	0.76
OSA	21%	5%	15%	46%	18.37	$<0.001^{b,c}$
T2D	21%	11%	13%	42%	13.26	0.001^{a}
MAP	95.4 (1.1)	94.2 (2.2)	95.0 (1.8)	97.2 (1.9)	0.55	0.58

Abbreviations: MCI, Mild Cognitive Impairment; BMI, body mass index; T2D, Type 2 diabetes; HTN, hypertension; HLD, hyperlipidemia; OSA, obstructive sleep apnea; GERD, gastroesophageal reflux disease; MAP, mean arterial pressure; NW, normal weight; OW, overweight; OB, obese. NOTE. Values reported as percentages for categorical variables and mean (SE) for continuous variables. The statistic is chi-square test of independence (2 degrees of freedom) for categorical variables and an ANOVA F statistic for continuous variables. Subscript b, indicates significant difference between NW and OB, c indicates significant difference between NW and OW.

The demographics data of subjects with and without T2D and OSA are presented in Table 1.3. Age and MCI-SV were similar between groups although education and MMSE score were lower in subjects with T2D. The NPI-Q mean total score was significantly higher in subjects with T2D and OSA. Further, the prevalence of moderate level NPI-Q symptoms differed based on the presence of T2D and OSA. Depression scores measured by the GDS were also

significantly higher for T2D subjects. There was no difference in age, education, MMSE, MCI-SV or GDS across OSA groups.

NPI-Q clusters

The prevalence and severity of specific NPI-Q clusters differed with respect to MCI subjects who were obese, and had T2D or OSA. The Hyperactivity cluster was the most frequent with 56% of subjects having at least one symptom. Figure 1.1A shows the frequency of each symptom cluster across groups. Affective symptoms significantly differed between OB and NW groups ($X^2_2 = 6.76$, $p = 0.03$). Subjects with sleep apnea also showed a significantly higher frequency of solely Affective symptoms ($X^2_1 = 5.39$, $p = 0.02$). Diabetic subjects had a significantly higher frequency across 3 clusters, Affective ($X^2_1 = 8.85$, $p = 0.003$), Hyperactivity ($X^2_1 = 14.19$, $p < 0.001$) and Psychosis ($X^2_1 = 3.74$, $p = 0.05$) symptoms. A posterior power analysis was then conducted to measure the strength of the association between obesity, T2DM, and OSA with each NPI-Q clusters. For our significant comparisons of OB and OSA with Affective symptoms had a power of 60% and 56% respectively. In addition, for each significant association of T2DM, as the cluster significance decreased, the power of the association increased: Psychosis, power = 50%, Affective, power = 86% and Hyperactivity, power = 98%.

The mean severity of NPI-Q clusters across groups is shown in Figure 1.1B. In OB subjects, Affective symptoms were also more severe ($F = 3.30$, $p = .04$) along with Psychosis cluster ($F = 4.55$, $p = 0.03$). Subjects with OSA also had a higher severity of Psychosis symptoms (Student's $t = 2.50$, $p = 0.02$) as well as Apathy (Student's $t = 2.17$, $p = 0.03$) compared to those without a sleep disorder. Two NPS clusters were more severe in diabetic subjects: Affective (Student's $t = 2.11$, $p = 0.04$), and Psychosis (Student's $t = 2.52$, $p = 0.02$); Apathy and Hyperactivity was unrelated to this condition.

TABLE 1.3. Demographic, cognitive and behavioral measures of T2D and OSA groups

Characteristic	BMI-related disorder	Disorder Present	Disorder Absent	Statistic X^2 or F	P value
Age (yrs.)	T2D	73.0 (1.25)	74.6 (0.87)	1.06	0.29
	OSA	72.7 (1.38)	74.7 (0.86)	1.07	0.287
Female, n (%)	T2D	12 (52.2)	40 (45.5)	0.33	0.57
	OSA	7 (30.4)	45 (51.1)	3.14	0.076
Education (yrs.)	T2D	13.3 (0.77)	14.9 (0.33)	2.01	0.047
	OSA	15.0 (0.86)	14.4 (0.33)	0.64	0.45
BMI (kg/m^2)	T2D	29.9 (1.08)	26.7 (0.47)	3	0.003
	OSA	30.65 (0.92)	26.52 (0.48)	3.95	< 0.001
MMSE	T2D	25.8 (0.36)	26.7 (0.19)	2.13	0.035
	OSA	26.74 (0.37)	26.40 (0.19)	0.83	0.411
MCI-Severity	T2D	-1.04 (0.15)	-0.86 (0.06)	1.21	0.23
	OSA	-0.73 (0.18)	-0.93 (0.06)	1.27	0.208
NPI-Q score	T2D	7.63 (1.18)	4.48 (0.62)	2.38	0.019
	OSA	7.75 (1.37)	4.59 (0.60)	2.23	0.028
≥ 1, n (%)	T2D	17 (89.5)	51 (76.1)	1.6	0.338
	OSA	14 (87.5)	54 (77.1)	0.84	0.505
≥ 4, n (%)	T2D	14 (73.7)	27 (40.3)	6.61	0.01
	OSA	11 (68.8)	30 (42.9)	3.5	0.061
GDS score	T2D	4.26 (0.87)	2.67 (0.26)	2.36	0.02
	OSA	3.76 (0.85)	2.77 (0.25)	1.12	0.274
≥ 1, n (%)	T2D	18 (94.7)	71 (85.5)	1.18	0.453
	OSA	18 (85.7)	71 (87.7)	0.06	0.812
≥ 4, n (%)	T2D	9 (47.4)	22 (26.5)	3.18	0.075
	OSA	8 (38.1)	23 (28.4)	0.74	0.389

Abbreviations: BMI, body mass index; MMSE, Mini-Mental State Examination; MCI-SV, MCI severity; GDS, Geriatric Depression Scale; NPIQ, Neuropsychiatric Inventory Questionnaire; T2D - type 2 diabetes; OSA, obstructive sleep apnea. NOTE. Results are presented as mean (SE) for continuous variables and n (%) for categorical variables. The statistic is chi-square test of independence (1 degree of freedom) for categorical variables and an independent samples t test, t statistic for continuous variables.

Discussion

In this study, we assessed the relationship of weight with specific NPS and the severity of cognitive impairment in MCI subjects. Our hypothesis was supported, in part, in that the frequency and severity of affective NPS were significantly higher in obese MCI subjects. To our knowledge, a direct examination of the relationship between BMI and NPS in MCI has not been reported, although the prevalence of each BMI group in our sample is similar to national averages of overweight and obese individuals in the adult US population [119]. While there is a growing body of literature on the effects of obesity on behavioral symptoms and cognition we sought to include in our analysis obesity related conditions which often occur co-morbidly[104] and are believed to share neuropathological commonalities. Interestingly, HTN, HL and GERD proved not to be significantly related to obesity in our sample; they were present in relatively equal proportions in all 3 BMI groups (although HL showed a definite trend toward increase). This likely speaks to the multifactorial nature of these conditions, such that the contribution of obesity is only one of several driving factors. Our results indicate that in MCI the combination of increased weight with T2D showed the greatest differences in behavioral disturbances in regards to total scores, symptom cluster frequency and severity as well as changes in global cognition.

In our sample of early stage MCI subjects, BMI and related health conditions demonstrated a significantly higher prevalence and severity of specific NPS. Previous studies have reported depression, anxiety and apathy symptoms as the most frequent NPS seen in MCI, among obese persons [87,120] as well as in subjects with T2D [121] and OSA [122]. Our study supports these findings in that the Affective cluster (depression, anxiety) was more frequent in subjects with OB, T2D and OSA compared to those that were NW/OW or without T2D and OSA. The Affective cluster was also rated with greater severity for OB and T2D subjects, which leads to

our main finding that that there is a relationship between depression, anxiety and obesity in MCI. For all groups the Psychosis cluster had a significant difference in mean severity although it was only more prevalent in the T2D group. A possible explanation may be that despite delusions and hallucinations constituting the least frequent symptoms in MCI [46,48], their presence in the early stage of cognitive impairment is perceived more severely by the informant. Further, the presence of nighttime behaviors in this cluster were most likely the driving factor: nighttime behaviors were the most frequent and severe individual NPI-Q symptom present in 42% of subjects. The Apathy cluster did not differ in frequency in any of the group comparisons; however it did have a higher severity only in OSA subjects. Higher apathy in relationship to daytime sleepiness has been shown in OSA subjects [123], which may explain the heightened severity rating when present in this group. Thus, when assessing MCI subjects with behavioral disturbances, consideration should be given to higher BMI and BMI-related health conditions, specifically T2D and OSA, as possible contributors to the presentation of NPS. Future research will be necessary to determine whether lifestyle interventions and treatment of weight related disorders affect the persistence and severity of NPS over time.

The link between weight-related health conditions and NPS is not well understood. As with similar findings between these health conditions and cognition, current research has begun to identify central inflammation as a possible mechanism. One theory postulates that weight gain modulates adipocyte function resulting in a higher secretion of pro-inflammatory markers that reach the brain and alter neuronal function, ultimately leading to alterations in neurocircuitry and neural plasticity. These changes affect brain regions such as the prefrontal cortex and cingulate gyrus, resulting in the presentation of neuropsychiatric symptoms [74]. Moreover, a recent animal study showed a possibly direct effect of obesity on dopamine receptor function resulting in

depression-like behaviors and alterations in reward circuitry [124]. In MCI, obesity is considered to be a chronic condition yet the time course of the indirect changes described by the mechanism of central inflammation is unclear. Further research is needed to understand whether weight-related brain changes present in conjunction with the onset of cognitive impairment or whether they act separately to promote the presentation of neuropsychiatric symptoms.

In contrast to our hypothesis, MCI severity was not associated with BMI or T2D and OSA groups. One explanation may be that MCI is defined by cognitive impairment and represents a transitional state with a narrow range of deficits. There is a cut-off to the severity that reflects mild cognitive impairments before one achieves psychometric criteria for dementia. Moreover our study subjects are diagnosed as MCI by a stringent criterion of -1.5 SD in at least one cognitive domain, which in other studies has been broader, (e.g., -1.0 SD in 2 cognitive domains). This difference in criteria may provide a more uniform assessment of overall MCI severity. Another possibility is that an overall severity score is not a sufficiently nuanced measure of cognitive status. Diabetes and OSA show greater cognitive deficits in executive function than memory. It may be more effective to measure individual cognitive domain severity in order to detect differences in the effects of disorders such as T2D, OSA and even OB. Finally, overall MCI severity may differentiate groups later in the disease course, which cannot be examined in a cross-sectional design. However, one research study showed that MCI subjects with at least one symptom on the NPI-Q or GDS, and lower initial cognitive status resulted in a more rapid development of dementia [102]. In our T2D subjects, general cognition measured by the MMSE was significantly lower ($p = .03$) while NPI-Q and GDS total scores were nearly doubled compared to subjects without T2D. This may indicate that MCI subjects with T2D and NPS ≥ 4 are at an increased risk for conversion to dementia.

A surprising finding of this study was the lower mean age of overweight and obese MCI subjects at the time of diagnosis by nearly 7 years. Middle age obesity promotes a higher risk of conversion to AD [125]. Since our data come from newly diagnosed MCI patients, this suggests that higher adiposity may cause an earlier emergence of cognitive impairment, likely through the burden of additional physiologic stressors. Further, an early onset of cognitive impairment in the obese may create a group of individuals susceptible to the onset of AD at an earlier age compared to those of normal weight. Despite many OB subjects having T2D and OSA, there was not a difference in the age at diagnosis based on these conditions. Isolating risk factors associated with weight may unmask features of the underlying pathological changes associated with prodromal AD.

Limitations

There are some limitations that must be taken into account in interpreting our results. First, this study is cross sectional and therefore does not assess cognitive and NPS status over time in relationship to BMI groups. For the same reason, it also cannot evaluate the direction of the association or capture the initiation and persistence of NPS. Second, due to the sample being a specialty referral clinical, genetic testing was not routinely done to establish apolipoprotein allele status, chronicity of overweight and obesity, or effectively capture socio economic status. In addition, our examination of NPI-Q symptomology was based on a score of ≥ 1, which is a very mild disturbance. However, recent studies have shown that even the measurement of the presence or absence of symptoms can predict disease progression [126]. In this regard, it is notable that large differences were seen in the frequency and severity of NPI-Q clusters with respect to BMI-related disorders T2D and OSA.

Lastly, in our analysis we did not have adequate power to detect some of our associations between OB and OSA with affective symptoms. The results provided in this article allow for the

generation of hypothesis for future work. This initial investigation provides new information about possible co-morbidities in MCI that can be replicated in a larger sample such as the Alzheimer's Disease Neuroimaging Initiative[127]. The current focus of this research group is to further analyze the relationships of NPS and OB in MCI using a more rigorous epidemiologic approach with subjects from the ADNI dataset. Future studies will focus on longitudinal follow-up to examine whether there is a relationship between weight, NPS prevalence and MCI severity at later stages of MCI and early AD, and also to establish whether a higher BMI produces a greater incidence of NPS over time.

Conclusions

This study demonstrates that within MCI, BMI and related disorders T2D and OSA showed a higher rate of psychopathologic changes, most particularly in the Affective, Hyperactivity and Psychosis clusters. Further, increased late life adiposity, which represented over 65% of subjects, was associated with a lower mean age at the onset of cognitive symptoms. Future research should focus on better understanding the intersection of NPS and OB in MCI, as well as the combined effect of these disorders and BMI-related disorders on the brain and clinical progression of MCI. In clinical settings, diabetic patients with MCI should be monitored for behavioral changes.

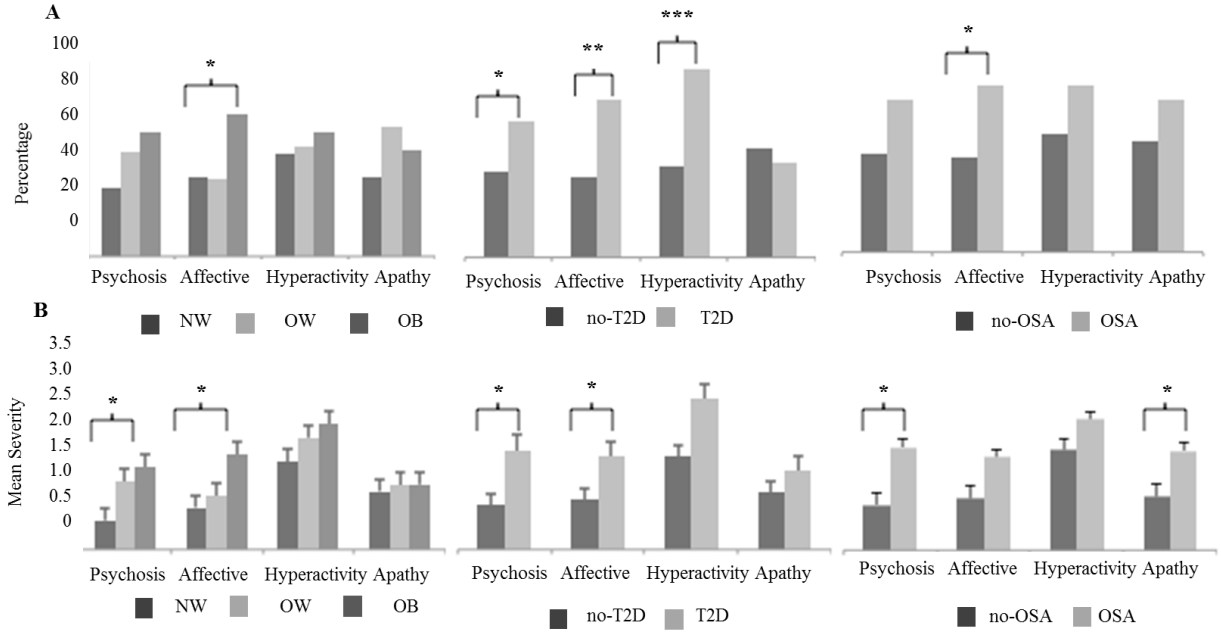

FIGURE 1.1. The NPI-Q cluster frequency and severity of BMI, T2D and OSA MCI subject groups. The 12 NPI-Q symptoms domains are clustered into 4 groups of, Hyperactivity (agitation, disinhibition, irritability, motor disturbances and euphoria), Apathy (apathy, appetite), Affective (depression, anxiety) and Psychosis (delusions, hallucinations, night-time behaviors). **A)** The frequency of each NPI-Q cluster is plotted for BMI, T2D and OSA groups. Cluster frequency statistics were conducted using the chi-square test of independence (2 degrees of freedom for BMI and 1 degree of freedom for T2D and OSA). **B)** The mean (SE) severity of NPI-Q clusters for BMI, T2D and OSA groups. Mean differences in cluster severity were compared using the analysis of variance (ANOVA) model for BMI and a student's t-test for T2D and OSA. Significant associations are marked as follow, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Abbreviations: NPI-Q, Neuropsychiatric Inventory Questionnaire; MCI, mild cognitive impairment; BMI, body mass index; T2D, type 2 diabetes; OSA, obstructive sleep apnea.

CHAPTER 2

THE EFFECT OF BODY MASS INDEX ON BRAIN STRUCTURE IN MILD COGNITIVE IMPAIRMENT

Introduction

Obesity is a growing epidemic affecting 30 million people worldwide and 38% of adults in the United States[128]. In the U.S., the rate of obesity is growing fastest among older adults ages 40 – 80. Obesity affects the peripheral and central nervous system resulting in an increased risk of metabolic syndrome, cognitive deficits, behavioral disturbances, and Alzheimer's disease (AD)[68,129]. Obesity also affects brain structure. Differences in brain volume have been shown in obese (OB) compared to lean controls[72,80,83]. A few studies have shown lower regional brain volume or decreasing volume over time for OB subjects across age groups[82,130,131] yet cognitive deficits in OB are not consistently present across young, middle and old age adults[132,133]. Previous research in aging studies have demonstrated a high body mass index (BMI) in midlife (45-65 years) correlating with increased cognitive impairment and a higher likelihood of developing dementia later in life[68,134], but high BMI in late life (>65 years) correlating with no changes in cognition and a slower progression to dementia[135,136]. This relates to the obesity paradox, which is defined as a counterintuitive relationship of obesity with a seemingly positive health outcome[135,136]. These findings indicate that there is an interaction of weight and age on cognition, and cognitive decline.

In mild cognitive impairment (MCI), an intermediate state between normal cognition and dementia[1], the effect of age and weight on brain structure has yet to be explored. All MCI subjects are at an increased risk for dementia[5]. Research on MCI subjects seeks to identify individuals at highest risk for conversion by assessing cognitive factors, biomarkers, and behavioral and metabolic influences. The combination of these factors makes MCI a heterogeneous group of individuals far beyond the three primary cognitive subtypes of amnestic (memory dominant), non-amnestic (non-memory, i.e. language) and multi-domain MCI. A

multipronged approach to understanding prodromal dementia states is necessary due to the possibility of multiple outcomes that reflect different underlying pathologies.

Research focusing on non-cognitive symptoms such as metabolic disorders (ie. obesity, type-2-diabetes, and hypertension) and general behavioral changes has grown rapidly over the last 10 years. Further, age and weight each affect the susceptibility to cognitive and structural brain changes. The age of onset of MCI ranges from 55-90 years and spans middle age to old age. There is nearly a 3-fold increase (Hazard ratio = 2.7) in the risk of dementia for middle age obese subjects with normal cognition[68,125,134]. However, in studies on patients later in life with MCI, low BMI results in greater cognitive decline over time. The apparent susceptibility of normal and underweight individuals to faster decline in MCI is not well understood. Based on previous research this study seeks to measure the relationship of weight and age on brain structure in order to find biological differences that might explain this relationship.

Mild cognitive impairment and obesity affect brain volume in specific brain regions. The majority of atrophic changes related to amnestic MCI are localized to the medial temporal lobe. Specifically, entorhinal cortex and hippocampus atrophy are sensitive measures of early amnestic impairment and are predictive of AD pathology[82]. Only one study has measured the effects of BMI on brain volume in a medium sized sample of MCI subjects. Ho et al measured the relationship of BMI and brain volume using a voxel based analysis of the whole brain. Their results indicated that as BMI increased, brain volume decreased within frontal, temporal and the parietal lobes. This complements research that has also found a negative correlation between BMI and brain volume in early adulthood and in older adults without cognitive impairments[80,137]. These studies found significant changes in whole brain volume, frontal lobe, occipital lobe and the temporal lobe (specifically the hippocampus) volume. Since decreased brain volume is a

biomarker for AD, lower brain volumes related to weight in MCI may make individuals more vulnerable to dementia.

The Alzheimer's disease Neuroimaging Initiative (ADNI) is a multisite longitudinal study that has collected research data from people with normal cognition, MCI and AD to better understand the development of AD[138]. The power of the ADNI lies in the thorough clinical, neuroimaging and biomarker data collected on now over 1,000 study volunteers, allowing for the analysis of critical questions related to understanding MCI and AD through the use of a large sample. More information on ADNI can be found in the Methods section.

For this study, the ADNI's processed volumetric MRI data, analyzed by ADNI researchers via the software FreeSurfer allowed for the comparison of region-specific brain volumes across BMI groups of MCI subjects[139]. Our main research question was: how does BMI relate to brain structure, if at all, in MCI subjects? Based on previous research in older adults and MCI subjects[72,80–82,137] we predicted that in MCI a higher BMI will correlate with lower brain volume.

Methods

Participants

Behavioral, height, weight, and MRI data were obtained from The Alzheimer's Disease Neuroimaging Initiative (ADNI) database[138] (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early

AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

ADNI subjects were recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these protocols have recruited over 1500 adults ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. Clinical, behavioral and neuroimaging data are collected for each patient with up to 54 months of follow up per patient. MRI methods, procedures and preprocessing by ADNI have been previously described[140] and can also be accessed at the following website: afni-info.org

Inclusion criteria for MCI set forth by ADNI, included; a MMSE score between 24 – 30, a subjective memory complaint by the patient or caregiver, objective memory loss measured by the Wechsler Memory Scale Logical Memory II, a global Clinical Dementia Rating (CDR) of 0.5, preserved activities of daily living, and the absence of dementia.

BMI groups

The MCI sample was grouped by traditional BMI criteria: normal weight (NW; BMI 18.5- 24.9 kg/m^2), overweight (OW; BMI 25 - 29.9 kg/m^2) or obese (OB; BMI $\geq$ 30 kg/m^2). Height (in inches) and weight (in pounds) measurements were taken at the time of clinical diagnosis of MCI. BMI was converted to the unit kg/m^2 using the follow calculation, [(Weight (lb.) / Height^2 (in.)) x 703].

ADNI imaging data acquisition

The ADNI MRI method protocol has been previously published[139]. Briefly, all subjects underwent whole-brain MRI scanning on 3-Tesla GE Medical Systems scanners, on at least one of two occasions (baseline and 6 months). T1-weighted IR-FSPGR (spoiled gradient echo) sequences (256×256 matrix; voxel size = 1.2×1.0×1.0 mm3; TI=400 ms; TR = 6.98 ms; TE = 2.85 ms; flip angle = 11°), were collected as well as diffusion-weighted images (DWI; 35 cm field of view, 128×128 acquired matrix, reconstructed to a 256×256 matrix; voxel size: 2.7×2.7×2.7 mm3; scan time = 9 min; more imaging details may be found at http://adni.loni.usc.edu/wpcontent/uploads/2010/05/ADNI2_GE_3T_22.0_T2.pdf).

ADNI FreeSurfer methods

Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications[141–154]. Briefly, this processing includes motion correction and averaging [153] of multiple volumetric T1 weighted images (when more than one is available), removal of non-brain tissue using a hybrid watershed/surface deformation procedure[152], automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles)[145,146] intensity normalization[155], tessellation of the gray matter white matter boundary, automated topology correction[144,156], and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class[141–143]. Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and

analysis including surface inflation[147], registration to a spherical atlas which is based on individual cortical folding patterns to match cortical geometry across subjects[148], parcellation of the cerebral cortex into units with respect to gyral and sulcal structure[149,157], and creation of a variety of surface based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface[143]. The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting sub millimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis[158] and manual measurements[159,160]. FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths[150,154].

FreeSurfer region of interest analysis

The regions of interest (ROI) output by FreeSurfer and made available on the ADNI website was downloaded for analysis of regional volumes across weight and age groups. Data was obtained from the UCSFFX spreadsheet of FreeSurfer Version 5.1. Subjects that had a non-accelerated T1 screening MRI, whose status was "complete" and had an overall quality check (QC) of "Pass" for all QC regions were included in the analyses. Brain regions that related to MCI and BMI were selected for analysis, resulting in 36 regions. Each brain region was corrected for the total intracranial volume to eliminate subject specific differences in brain region volumes that are related to total brain size. The corrected value for each brain region per subject was then used for statistical analysis.

Statistical analysis

Regional brain volumes, behavioral, and clinical data of MCI subjects at screening or baseline was downloaded from the ADNI database. The main comparison groups were BMI categorized as normal weight (NW, BMI: <25 kg/m^2), overweight (OW, BMI: 25 – 29.9 kg/m^2) and obese (OB, BMI: > 30 kg/m^2). Thirty-six cortical and subcortical regional brain volumes were selected due to previously reported relationships with either BMI or MCI and averaged between hemispheres. The raw brain volumes were corrected for head size by dividing by the total intracranial volume (ICV). An analysis of variance (ANOVA) model was used in each experiment to compare cognitive and behavioral scores, and regional brain volumes across BMI groups. A multivariate ANOVA model corrected for age and education. Lastly, a correlation analysis measured the relationship of brain volume with BMI, age, MMSE, CDR-sum of boxes (CDR-SB) scores.

Results

Participants

The MCI sample consisted of 635 subjects with baseline regional brain volume measures. The BMI groups consisted of 216 (34%) NW, 282 (44%) OW and 137 (22%) OB. Two underweight subjects with a BMI of 17.64 and 17.85 were included in the normal weight group. Overall, the MCI cohort had a mean BMI of 27.1, age of 71.9 years, education of 15.9 years, and 43% were female. Obese subjects were significantly younger than NW, with lower educational attainment and a higher mean GDS score. Age and BMI values were negatively correlated ($r = -0.144$, $P < 0.001$). There were 140 Middle Age (age between 55 and 65) subjects and 494 Seniors (age greater than 65). The demographic characteristics of the MCI subjects as whole and by BMI groups are reported in Table 2.1.

Brain volume

Baseline regional brain volumes were compared across BMI groups to determine whether there was a difference in mean brain volumes. First, a MANOVA model measured the main effect of BMI on regional brain volumes. There was a statistically significant difference in brain volume across BMI group, $F (72, 1194) = 1.36$, $p = 0.026$; Wilks'$\Lambda = 0.854$, partial $\eta^2 = 0.08$. Next, age and education were added as covariates, based on previous research indicating their relationship with brain volume. In this full factorial model, BMI, age and education were all independent significant contributors to volume differences in the overall multivariate tests (BMI: $F (72, 1186) = 1.31$, $p = 0.048$; Wilks'$\Lambda = 0.858$, partial $\eta^2 = 0.07$; Age: $F (36, 593) = 9.17$, $p < .005$; Wilks'$\Lambda = 0.642$, partial $\eta^2 = 0.36$; Education: $F (36, 593) = 2.15$, $p < .005$; Wilks'$\Lambda = 0.885$, partial $\eta^2 = 0.12$). In the full factorial model, 14 (out of 36) regions significantly differed by BMI. Each of the regions that significantly differed are displayed in Figure 2.1.

TABLE 2.1. Demographic, cognitive, functional and behavioral measures for all MCI subjects and for each BMI group

Characteristic	All MCI N = 635	NW N = 216	OW N = 282	OB N = 137	Statistic F or X^2	P value
Age (yrs)	71.89 (7.46)	73.03 (7.22)	71.94 (7.41)	69.95 (7.60)	7.34	0.001[a, b]
Female, n (%)	272 (43%)	107 (50%)	108 (38%)	57 (42%)	6.52	0.038[b]
Education (yrs.)	15.89 (2.88)	16.43 (2.79)	15.73 (2.85)	15.38 (2.94)	6.52	0.002[a, b]
MMSE score	27.62 (1.82)	27.52 (1.84)	27.60 (1.84)	27.80 (1.75)	0.983	0.375
CDR-SB	1.52 (0.86)	1.49 (0.82)	1.53 (0.89)	1.54 (0.89)	0.162	0.850
NPI-Q score	2.33 (3.23)	2.05 (3.26)	2.24 (2.96)	2.97 (3.62)	3.32	0.037[c]
GDS score	1.69 (1.47)	1.65 (1.46)	1.57 (1.34)	2.02 (1.58)	4.54	0.011[d]

Values are presented as mean (SD) for continuous variables and number (%) for categorical variables. Data are analyzed via analysis of variance (ANOVA) model. Superscripts indicate the direction of the differences after Bonferroni method correction: a = NW > OB, b = NW > OW, c = OB > NW, d = OB > OW. Statistical significance is set at $p < 0.05$.

For all significant comparisons, brain volume was lowest for NW subjects. Table 2.2. lists the regions that significantly differed and the mean raw volume measures for each BMI group. A follow-up correlation analysis confirmed a positive association of BMI with brain volume. As expected, age was negatively associated with volume in each region. The correlation between precuneus volume and BMI (Pearson's $r = .159$, $p < .001$) and age (Pearson's $r = -.391$, $p < .001$) are displayed in Figure 2.2. In addition, while neither MMSE nor CDR-SB differed by BMI in the ANOVA, the brain volumes of all 14 significant regions were positively correlated with the MMSE and 12 out of 14 were negatively correlated with the CDR-SB. This indicates the expected cognitive and functional relationship, in that, as brain volume increases MMSE

scores increase and CDR-SB scores decrease (moving toward normal cognitive and functional abilities).

TABLE 2.2. Significant cortical and subcortical volume differences across BMI groups of MCI subjects

	Volume (mm^3)				
Brain Region	Normal Weight n = 216	Overweight n = 282	Obese n = 137	F	P value
Precuneus	8005 (1217)	8455 (1197)	8596 (1339)	7.33	0.001[a,b]
Middle temporal gyrus	9487 (1485)	9946 (1486)	101743 (1409)	5.26	0.005[a,b]
Hippocampus	3226 (537)	3432 (554)	3565 (619)	5.14	0.006[a,b]
Lingual gyrus	5662 (924)	5976 (989)	6084 (894)	5.06	0.007[b]
Lateral occipital cortex	10099 (1602)	10554 (1523)	10678 (1674)	4.90	0.008[b]
Amygdala	1254 (247)	1331 (243)	1363 (233)	4.89	0.008[a,b]
Rostral anterior cingulate gyrus	2048 (404)	2164 (390)	2160 (425)	4.04	0.018[b]
Superior parietal lobule	11052 (1606)	11549 (1709)	11943 (1913)	3.69	0.026[a]
Isthmus cingulate gyrus	2148 (380)	2250 (392)	2317 (381)	3.63	0.027
Insular cortex	5965 (847)	6226 (830)	6279 (851)	3.56	0.029[b]
Pericalcarine cortex	1837 (343)	1938 (370)	1958 (317)	3.47	0.032[a,b]
Medial orbitofrontal gyrus	4103 (698)	4325 (727)	4424 (713)	3.46	0.032[b]
Inferior parietal lobule	11329 (1822)	11852 (1876)	12061 (1858)	3.30	0.038[b]
Banks of the superior temporal sulcus	2109 (342)	2219 (369)	2219 (386)	3.26	0.039[b]

Raw brain volumes, mean (SD), for regions that significantly differed by BMI in a MANOVA model- BMI; NW (n = 216), OW (n = 281), OB (n = 137). The statistic is a multivariate general linear Model (GLM), factored by BMI group, with covariates age, and education. Superscripts indicate the direction of the differences after pairwise comparison correction using the Bonferroni method: a = NW < OB, b = NW <OW (analysis was done using brain volumes corrected for total intracranial volume). Significant was set at $p < 0.05$.

Next, we further examined the relationship of age and BMI with brain volume in our sample by conducting a series of post-hoc analyses to determine whether age might be a

confounding variable to our results. For both the Middle Age and Senior groups brain volume increased as BMI increased. Body mass index and age values had a significant yet weak association (Pearson's r = -0.146, p < .001). Further, a two-way ANOVA tested the interaction of BMI (NW, OW, OB) and age (Middle-aged, Senior), was not significant, F (72, 1180) = 0.75, p = 0.939; Wilks'Λ = 0.914, partialη^2 = 0.044. Further, we separated the Middle-age and Senior groups and ran a MANOVA controlling for age and education to examine the effect of BMI on brain volume within these two distinct life stages. In the model of only middle-aged subjects there was no difference in any of the 36 brain regions examined based on BMI group. However, we found robust effects for brain volume differences by BMI in the Senior group. In addition, despite the large age range for the Senior group (range = 55 – 89 years) there was not a difference in age across BMI groups. For Seniors, all of the original 14 regions remained significant, plus three additional regions; the fusiform gyrus (F= 3.51, p = 0.034), parahippocampal gyrus (F = 3.37, p = 0.035), and the superior temporal gyrus (F = 4.5, p = 0.012). Additional post hoc analyses included BMI, age and brain volumes were also entered into a multiple regression analysis with the goal of assessing the relationship of BMI and brain volumes with and without age added into the model. In preparation for this analysis the Durbin-Watson test was run to determine whether there was independence between residuals in the model. This test did not meet the threshold of approximately 2.0 and further analyses could not be completed due to the higher correlation among our variables (age, BMI, brain volume). Finally, one third of the population was randomly removed to test whether the large size of our sample may have generated false positive data. Within the reduced sample, with covariates added, there was not an effect of BMI on brain volumes, F (72, 770) = 1.09, p = 0.295; Wilks'Λ = 0.824, partial η^2 = 0.09. The reduction of the sample did not affect the observed power of the analysis, power = 0.998.

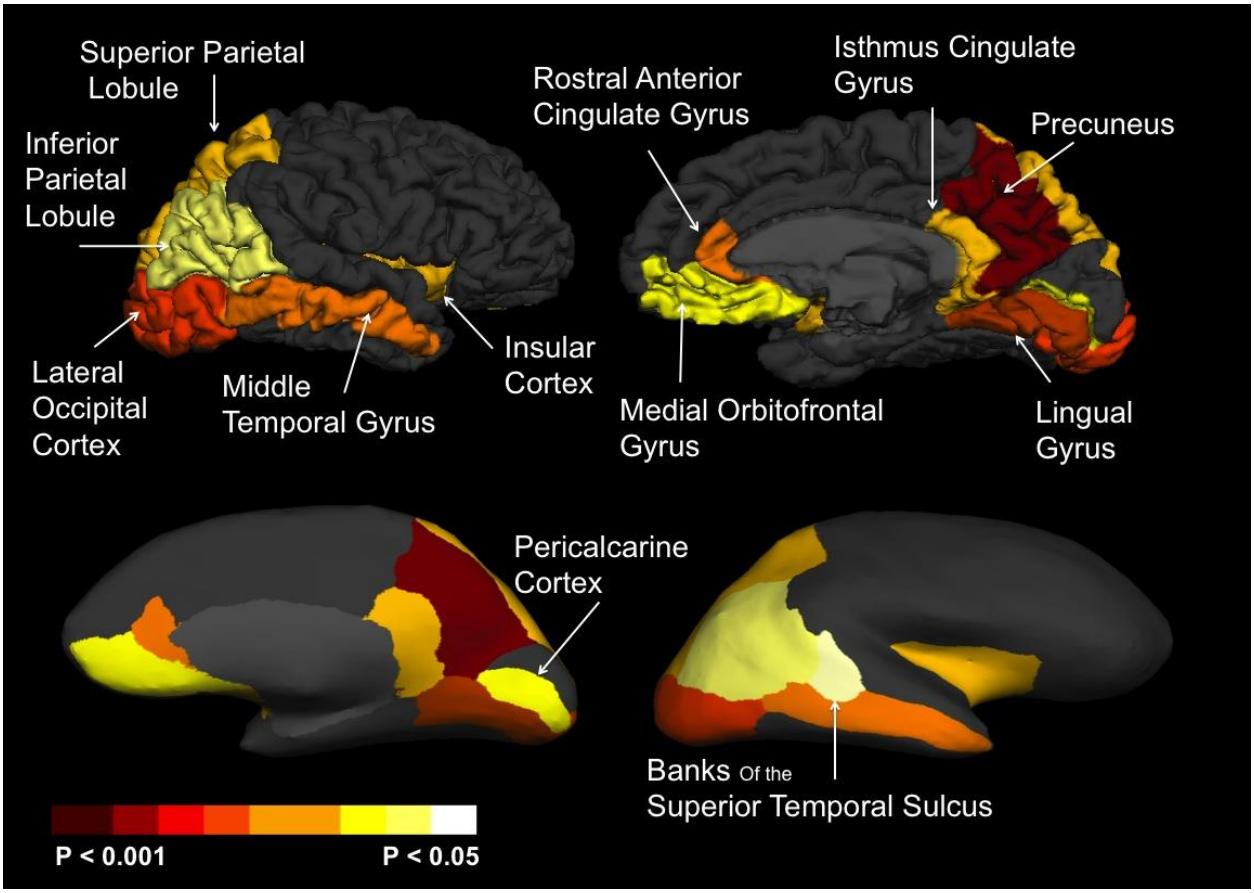

FIGURE 2.1. Cortical brain regions that significantly differed in volume by BMI. Subcortical regions that also differed by BMI are not shown: the hippocampus ($F = 5.1$, $p = .006$) and amygdala ($F = 4.9$, $p = .008$). The effects of BMI on brain volumes were analyzed using a MANOVA model correcting for age and education. Regions range in their significance with light yellow regions meeting statistical significance of $p < 0.05$ and dark red having a p value of $p < 0.001$.

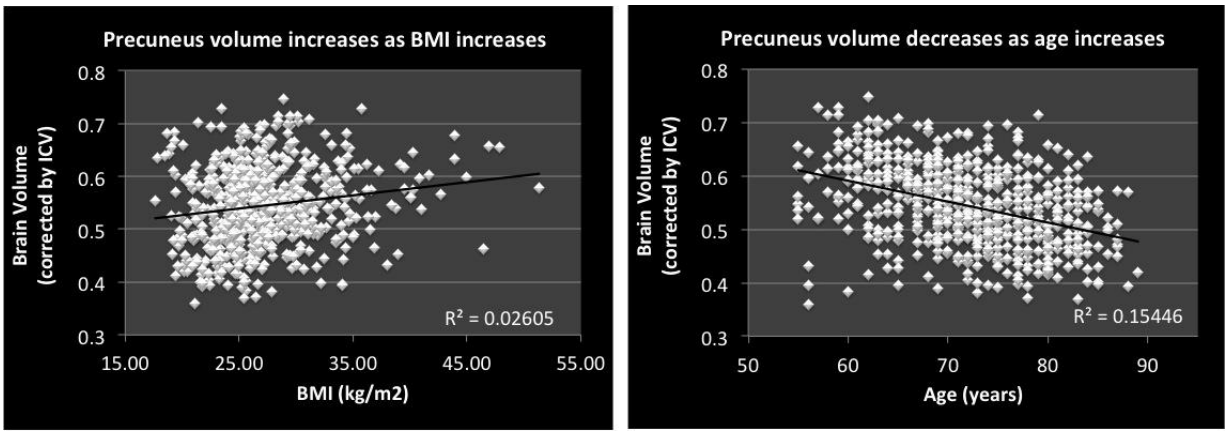

FIGURE 2.2. The correlation of precuneus volume with BMI and age. BMI was positively associated with precuneus volume whereas age was negatively associated. The associations were measured using a Pearson's correlation with significance set at $p < 0.05$.

Discussion

This study is the first to provide neurological evidence for the possible association of a normal BMI with lower brain volumes in MCI. We predicted that as BMI increased, brain volume would decrease. Yet, in our sample, the NW subjects showed statistically lower brain volumes. Obese subjects had less education, were younger, with higher mean NPI-Q and GDS scores. There were 14 regions (out of 36 preselected cortical and subcortical regions) that showed a medium effect of BMI on brain volume and, in all regions, raw and corrected volumes were lowest for NW subjects compared to OW and OB subjects. This is the largest MCI study on the relationship of weight and brain structure, with over 600 MCI subjects.

Previous studies investigating the effect of BMI on brain volume in cognitively normal adults have found obesity to result in lower brain volumes and worse cognitive performance[161]. One study in older women found frontal, posterior parietal and occipital regions to be specifically vulnerable ROIs in obesity; along with cognitive deficits in executive function that were associated with smaller left orbitofrontal gyrus volume[72]. In elderly men and women, BMI was negatively correlated with brain volume in the orbitofrontal cortex, anterior cingulate gyrus

and the medial temporal lobe[80]. Across these studies whole brain volume also decreased as BMI increased[80,82,162] . Possible mediators between a high BMI and brain atrophy include inflammation[163], Type 2 diabetes[164], and hypercortisolemia[165]. While the link between BMI and brain volume is not likely to be direct there may be one or more mediators that play a role in this relationship and in MCI the underlying pathology may initiate the opposite responses seen in older obese adults with normal cognition.

The only other study on BMI and brain volume in MCI found that brain volume decreased by 1% for every 1-point increase in BMI[82]. The difference between this study's findings and our own is most likely due to different methodologies. In our study, subjects were grouped by BMI, and ROI mean volumes were compared, whereas Ho et al., used a whole brain voxel based analysis of ADNI MCI subjects (ADNI-1, n = 399) with the addition of 77 subjects from the Pittsburgh Cardiovascular Health Study-Cognition Study (CHS-CS). Our study had a larger ADNI sample using all 3 phases of only amnestic MCI subjects, and specifically compared regional brain volumes related to both MCI and obesity. The hypothesis of this study was created in tandem with the available evidence for the effects of BMI on brain volume outlined above, yet our findings provide new insight into the relationship of weight and BMI in MCI.

Our findings were similar in the brain regions affected by BMI however; we found the opposite relationship of BMI and brain volume (volume decreased as BMI decreased). The brain regions affected by a low BMI primarily constituted the parietal and occipital lobes of the brain. The parietal lobe functions primarily in the integration of sensory information and the occipital lobe in vision. Specifically, the parietal lobe functions in somatosensory and tactile function (postcentral gyrus), motility (precuneus and superior parietal lobule), spatially directed attention (R-inferior parietal lobe), symbolic thought and memory (L-inferior parietal lobe) and memory

vision and proprioception (inferior parietal lobe, posterior parietal gyrus)[166]. The occipital lobe functions in visual perception, including object motion, face recognition, and visual control of skilled actions. The pathological stages of Alzheimer's disease described by Braak and colleagues, indicate involvement of occipital and parietal lobe regions in Stages II – IV of the disorder (for amyloid), or early to moderate Alzheimer's disease.

Our findings suggest that the pattern of regional brain volume reductions in NW MCI may indicate a more severe state of MCI with early deficits in brain regions that reflect middle to late stage Alzheimer's disease. Normal weight subjects may have smaller brain volumes compared to OW and OB in our sample, yet, the most likely explanation is due to the older age of NW subjects. Additional post hoc analyses were conducted including the separate analysis of middle-age and Senior groups, multiple regression, random removal of one third of the sample to address the possible confounding of age that may have persisted despite correction in the MANOVA model. These post-hoc analyses showed a loss in the effect of BMI on brain volume. Future studies that aim to assess the relationship of BMI and brain volume in MCI should be designed so that there is an equal representation of middle-age and Senior subjects. In addition, study designs should focus on specific age groups with a limited age range of 5 years; this will more effectively address the possible confounding of age on brain volume, and difference in age related brain atrophy that occurs in middle age to Senior stages (increasing from 0.5 to 1% atrophy per year after age 70).

While our initial findings contradict studies on regional brain volumes in normal cognition and MCI obese subjects, they align with many longitudinal studies that demonstrate a low BMI resulting in shorter progression time from MCI to AD dementia[81,167–170]. Current research demonstrates an increased risk of developing dementia in normal or underweight MCI subjects and a protective effect or decreased risk of dementia in overweight and obese subjects.

A longitudinal study of brain volume trajectories of older adults who were obese at middle age showed no change in whole brain volume over time and significant regional change only in the cingulate gyrus[81]. Tolppanen and colleagues also found that a decrease in BMI from midlife to late life increased the risk of AD (HR = 1.14)[170]. Our study is the first to provide neurological evidence for the findings listed above. The increased risk of dementia and shorter progression time of NW-MCI subjects may be due to lower regional brain volumes that extend beyond regions initially affected by MCI but of those that represent AD as shown in the present study.

Limitations

Some limitations must be taking into account when interpreting the results of this study. The main analysis examined the effect of BMI on brain volumes in brain regions related to high adiposity and MCI. There was a strong association between age and brain volume and in our sample, as BMI groups significantly differed by age. We controlled for age in our MANOVA model to address any potential confounding effects of age on our results[171]. When we did this the p-value for the model increased, from $p = .027$ to $p = 0.048$ and the effect decreased from a partial $\eta^2 = 0.08$ to partial $\eta^2 = 0.07$. Despite this, our analysis had adequate power (observed power = 1.0) and remained statistically significant, which may indicate a true effect of BMI on brain volumes. However, the interpretation of our results must be made with caution due to the high correlation of our variables (BMI, age, and regional brain volumes) within our analysis and the loss of a BMI effect in post hoc analyses.

Conclusions

Normal weight MCI subjects were unexpectedly older with lower regional brain volumes compared to OW and OB subjects. This study may provide neurological evidence for recent findings of a protective effect of a high BMI on MCI progression, and an increased likelihood of NW individuals progressing to dementia. However, further research is needed to elucidate the effects of age on brain volume separate from that of BMI on brain volume in MCI subjects. As the population of older adults increase, the number of overweight and obese people is expected to grow proportionally. Many seniors are surviving to older ages despite their weight; this is likely due to evolving treatments for conditions often comorbid with increased weight such as type-2-diabetes, cardiovascular disease and hypertension. The survivorship of overweight and obese adults increases the susceptibility of MCI and AD to a wide range of BMIs. It will be necessary to understand how weight effects or alters the pathophysiology of AD. Understanding the interactions of weight, age and brain structure may be important in assessing neurologic vulnerability and dementia risk in individuals with MCI.

APPENDIX

APPENDIX

TABLE 2A. Selected FreeSurfer brain regions for volume analysis across BMI groups

No.	Label	Region Name	No.	Label	Region Name
1	ParOrbital	Pars orbital cortex	19	PostCing	Posterior cingulate gyrus
2	ParOperc	Pars opercularis cortex	20	SupPariet	Superior parietal lobule
3	ParTriang	Pars triangularis cortex	21	SupTemp	Superior temporal gyrus
4	ParaHipp	Parahippocampal gyrus	22	Supramarg	Supramarginal cortex
5	MidTemp	Middle temporal gyrus	23	TempPole	Temporal pole
6	InfTemp	Inferior temporal gyrus	24	TransTemp	Transverse temporal cortex
7	ParaCent	Paracentral lobule	25	Bankss	Banks of the superior temporal Sulcus
8	PostCent	Postcentral gyrus	26	Cuneus	Cuneus
9	RostAntCing	Rostral anterior cingulate gyrus	27	Entorhinal	Entorhinal gyrus
10	CaudAntCing	Caudal anterior cingulate gyrus	28	FrontPole	Frontal pole
11	Insula	Insular cortex	29	Fusiform	Fusiform gyrus
12	CaudMidFront	Caudal middle frontal gyrus	30	InfPariet	Inferior parietal lobule
13	RostMidFront	Rostral middle frontal gyrus	31	IsthCing	Isthmus cingulate gyrus
14	Precuneus	Precuneus	32	LatOrbFront	Lateral orbitofrontal gyrus
15	LatOccip	Lateral occipital cortex	33	Lingual	Lingual gyrus
16	PreCent	Precentral gyrus	34	MedOrbFront	Medial orbitofrontal gyrus
17	SupFront	Superior frontal gyrus	35	Amygdala	Amygdala
18	Pericalcar	Pericalcarine cortex	36	Hipp	Hippocampus

The full list of selected regions from the FreeSurfer software are indicated in the table above by their label name in FreeSurfer and the full anatomical name of each region.

CHAPTER 3

THE INTERACTION OF BODY MASS INDEX, NEUROPSYCHIATRIC SYMPTOMS AND AGE IN MILD COGNITIVE IMPAIRMENT: A LONGITUDINAL STUDY

Introduction

A growing number of Americans have Alzheimer's disease, and the prevalence will dramatically increase over the next 30 years. The pathological process of Alzheimer's disease is a long trajectory of physiological, behavioral and cognitive changes that begin many years prior to clinical symptoms of dementia[172]. Prior to meeting clinical criteria for dementia, patients experience an intermediate stage of mild cognitive impairment (MCI) that is characterized by mild cognitive and behavioral deficits[5]. Many factors predict the conversion from mild cognitive impairments to dementia. The majority of studies on these risk factors focus on cognitive changes and their relationship with progression from MCI to dementia. However, there are non-cognitive factors that predict the development of dementia[50,164]. These non-cognitive conditions are of great interest because they may provide an indication of early changes that are not directly related to the irreversible pathological stream that predates cognitive dysfunction. Of even further interest are those that are 'modifiable', which include conditions that involve lifestyle factors such as, diet and exercise. Two non-cognitive factors that fit these criteria and are prevalent in MCI are neuropsychiatric symptoms (NPS) and obesity. When MCI subjects have high NPS (>4) in the early stages of MCI, they show greater cognitive deficits and a higher rate of conversion to dementia[101,102]. An increased risk for dementia is also true for individuals that are obese in middle age (45 – 65 years old) with normal cognition[68,134]. Obesity and NPS often occur co-morbidly across age groups in individuals with normal cognition[74,173]; however, the association of these two factors with MCI progression to AD has not been measured.

Neuropsychiatric symptoms are highly prevalent in AD (70-90%) and in MCI (40 – 60%)[52,102]. MCI subjects with high NPS scores are 2.5 times more likely to develop dementia and also show a faster rate of cognitive decline[47]. Further, when NPS burden worsens over time individuals demonstrate faster cognitive and functional decline, and progression to AD over 2

years[174]. Depression, anxiety and apathy are highly prevalent in obese individuals with normal cognition[87,90]. MCI subject who are obese with high NPS may be at an increased risk for cognitive decline.

The number of longitudinal studies investigating BMI in MCI continues to grow with a primary focus on cognition function[175] and the risk of conversion to dementia[168,169] over one and two year intervals. Research findings indicate that a high body mass index (BMI) in MCI does not result in increased cognitive deficits or a higher conversion rate to dementia. Many findings identify an increased risk of cognitive decline and the development of dementia in normal weight MCI subjects [125,169]. In these studies normal weight subjects have greater cognitive decline than over-weight and obese subjects, demonstrated by tests of global cognition, the mini mental status exam (MMSE) and Alzheimer's disease assessment scale – cognitive (ADAS –cog scores)[176]. The risk of developing dementia is increased 2.5 times in MCI subjects with a low baseline BMI whereas being overweight reduces the risk of developing dementia over 2 years[177] Further, weight loss also increases the risk of cognitive changes. Cognitively normal elderly are more susceptible to MCI after weight loss[178], and in MCI the risk of dementia is increased by 3.4 fold and AD specifically by 3.2 fold with weight loss[179]. The findings of these studies may seem surprising at first in that, one would expect obesity to lead to more cognitive and functional dysfunction; yet, being overweight is protective against the onset of dementia. Because the link between obesity and AD has only been demonstrated when obesity is present at middle age, the relationship between increased weight and cognitive decline represents a paradox with age as its nexus[135,136]. Previous studies have measured cognitive changes and progression to dementia across BMI groups. This study will add to previous research by measuring the interaction of BMI and NPS within age groups of Middle Age and Senior subjects.

Recent work in our lab on MCI subjects near the time of diagnosis has shown that those who were obese had a higher frequency of affective neuropsychiatric symptoms (NPS) than normal weight subjects. Further, increased adiposity measured by BMI was associated with a younger age at onset of MCI by 7 years on average compared to normal weight subjects. Currently, no studies have investigated longitudinal changes in cognitive, functional and behavioral scores. This study seeks to address this gap in knowledge and provide evidence for specific cognitive and functional changes that may be related to BMI, age, and NPS in MCI. While we expect to see greater cognitive changes in the NW groups similar to previous reports, we sought to validate the obesity paradox in this context by directly comparing Middle Aged and Senior groups who have MCI. We hypothesize that the Middle Age obese group will show a faster progression to Alzheimer's type dementia than normal and over-weight middle-age subjects.

Methods

Participants

Demographic and behavioral data of MCI subjects were obtained from The Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu)[127]. The ADNI was launched in 2005 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of early AD progression is intended to aid

researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

ADNI subjects were recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these protocols have recruited over 1500 adults ages 55 to 90, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. Clinical, behavioral and neuroimaging data are collected for each patient for up to 54 months. MRI methods, procedures and preprocessing by ADNI have been previously described[140] and can also be accessed at: www.afni-info.org. Inclusion criteria for MCI set forth by ADNI include; an MMSE score between 24 – 30, a subjective memory complaint by the patient or caregiver, objective memory loss measured by the Wechsler Memory Scale Logical Memory II, a global Clinical Dementia Rating (CDR) of 0.5, preserved activities of daily living, and the absence of dementia.

For our study, we abstracted data on individuals who met ADNI-defined MCI criteria from all 3-phases of ADNI. Overall, the analysis was undertaken in two parts, first by conducting a longitudinal analysis that analyzed baseline, 2-year and change scores (2-yr – bl) on the NPI-Q, GDS, MMSE, ADAS-cog 13 and CDR-sb. Second, by determining the number of subjects that progressed to AD and examining the survival of subjects based on group membership in BMI (NW, OW, OB) or age (Middle-Age and Senior) group. Only MCI subjects with cognitive, behavioral and functional measures at both baseline and 2-year time points were included in the longitudinal analysis. We also analyzed whether there was an interaction of age with BMI groups and how NPS affected progression over 2 years.

Factors

We sub-divided our sample into a Middle Age group, aged 55 – 65 and a Senior group who were 66 years of age or older. We also created BMI groups as follows: normal weight (NW; BMI 18.5- 24.9 kg/m^2), overweight (OW; BMI 25 - 29.9 kg/m^2) or obese (OB; BMI ≥ 30 kg/m^2). Height (in inches) and weight (in pounds) measurements were taken at the time of clinical diagnosis of MCI. BMI was converted to the unit kg/m^2 using the follow calculation, [(Weight (lb.) / Height^2 (in.)) x 703].

Longitudinal analysis methods and statistical analyses

The longitudinal analysis assessed changes in cognitive, functional and behavioral measures over a 2-year interval. Global cognitive measures included the MMSE, and ADAS-cog 13. The MMSE assesses changes in 5 categories: orientation (i.e. date, place), registration or immediate recall, delayed recall, attention and calculation (i.e. subtraction) and language[27]. There are 30 questions worth 1 point each with scores ranging from normal cognition (>25) to severely impaired (≤ 10). In addition, the ADAS cognitive 13-item subscale tests cognitive domains of memory, language, praxis, attention, and other cognitive abilities with a total scoring range of 0 – 70 points[118]. Higher scores indicate a higher degree of impairment. Clinical Dementia Rating Scale – sum of boxes (CDR-SB)[180] scores were compared across groups as an additional measure of combined cognitive and functional change. The CDR-SB includes five categories, memory, orientation, judgment, community affairs, home and hobbies, and personal care that are assessed with item scores ranging from no impairment (0), mild impairment (0.5) up to severe impairment (3). The sum of each category score resulted in the total sum of boxes score, which could range from 0.5 to 15.

Neuropsychiatric symptoms were measured using the Neuropsychiatric Inventory Questionnaire (NPI-Q) [109] and the Geriatric Depression Scale –short form (GDS) [110]. The NPI-Q is a validated measure for assessing behavioral disturbances across 12 different domains in a

brief caregiver-reported questionnaire [109]. These include; delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, sleep and nighttime behavioral changes, and appetite and eating disorders. An informant familiar with the subject reports NPI-Q symptoms, by rating each symptom for their presence (yes/no), and severity (range of 0 - 3) for each item. Behavioral changes reported on the NPI-Q reflect symptoms present within one month of testing, with 36 possible points. The self-reported 15-point GDS scale further quantified depressive symptoms. Low NPS was designated as a total score between 0-3 symptoms and high NPS as ≥ 4 on either test.

The total score for each test and the prevalence of mild and moderate symptoms were measured across BMI and age groups. A difference score was computed between the baseline and two-year visit for each test and analyzed across all subjects and BMI groups. The difference in baseline, 2 year, and change scores were compared across BMI groups using an ANOVA model. A Bonferroni post-hoc test was used to determine which groups differed from each other. Significance was set at $p < 0.05$.

Survival analysis methods and statistical analyses

A survival analysis[181] was used to measure the survival distribution of BMI, age and NPS groups in order to identify differences in cumulative survival over two years related to these conditions independently and when factored together. The survival analysis included the following parameters: the time of origin was the baseline visit, the event was a dementia (probable AD) diagnosis, and the comparison groups were BMI (NW, OW, OB), age group (Middle-Age, Senior) and NPS (High/ Low baseline NPI-Q and GDS score). The survival distributions were measured for each group independently and factored together. Time was measured in 6-month intervals from the baseline visit to the 2-year visit. Censored events included loss to follow-up,

death, and another diagnosis. All ADNI MCI subjects that met the inclusion criteria were included in the survival analysis.

The cumulative survival of MCI subjects was calculated using Kaplan-Meier plots in SPSS version 22.0 (Chicago, IL). Significance was set at $p < 0.05$.

Results

Baseline measures for all ADNI MCI subjects from each phase were combined into one dataset. Selected demographic information for the combined dataset is displayed in Table 1. Overall, the sample was predominantly Caucasian, with nearly 16 years of education and over 66% were overweight or obese. The obese group was younger, less educated, with higher mean arterial pressure (MAP) values and a higher proportion of T2D, HTN, HLP and OSA co-morbid conditions compared to normal weight. Obese subjects also had higher mean NPI-Q scores and symptom prevalence compared to NW subjects. Age group differences in demographic, cognitive and behavioral variables are reported in the Appendix, Table 3A.

TABLE 3.1. Demographic, cognitive and behavioral characteristics for all ADNI MCI subjects and across BMI groups

Characteristic	All MCI (n =956)	NW (n = 318)	OW (n = 430)	OB (n = 205)	F or X^2	p value
Female, n (%)	396 (41.5%)	162 (50.9%)	144 (33.6%)	90 (43.9%)	23.3	0.015[c]
Age, yrs	72.51 (7.9)	73.47 (7.8)	72.68 (7.7)	70.68 (8.1)	8.1	< 0.01
MidAge, n (%)	199 (20.8%)	51 (16%)	88 (20.5%)	59 (28.8%)	12.3	0.002[c]
Senior, n (%)	756 (79.2%)	267 (84%)	341 (79.5%)	146 (71.2%)	12.3	0.002[c]
Education, yrs	15.93 (2.8)	16.49 (2.8)	15.84 (2.72)	15.22(2.9)	13.4	< 0.01
MMSE	27.57 (1.8)	27.46 (1.8)	27.57 (1.8)	27.75 (1.7)	1.7	0.19
CDR-SB	1.54 (0.9)	1.55 (0.9)	1.53 (0.9)	1.56 (0.9)	0.1	0.88
BMI (kg/m2)	27.06 (4.7)	22.59 (1.8)	27.09 (1.4)	33.9 (4.0)	-	< 0.01
NPI-Q score	2.26 (3.1)	2.0 (3.1)	2.16 (2.9)	2.26 (3.2)	5.6	0.010[b]
≥ 1	494 (62.2%)	157 (58.4%)	223 (62.5%)	113 (69.8%)	5.6	0.021[c]
≥ 4	183 (23.2%)	53 (19.7%)	82 (23%)	47 (29%)	4.9	0.034[c]
GDS score	1.69 (1.5)	1.64 (1.5)	1.6 (1.42)	1.97 (1.8)	4.4	0.059[b]
≥ 1	730 (76.4%)	242 (76.1%)	326 (75.8%)	161 (78.9%)	0.8	0.053[c]
≥ 4	128 (13.4%)	40 (12.6%)	50 (11.6%)	38 (18.6%)	6.1	0.122[c]

Mean comparisons across BMI groups were conducted using an ANOVA model for continuous variables, mean (SD) and the chi-square test of independence for categorical variables, n (%). Behavioral tests are reported as the mean score and total symptom categories of ≥1 or ≥4. [b] Non-parametric Kruskal-Wallis Test [C] Gamma approx p value, ordinal by ordinal. Significance was set at $p < 0.05$.
Abbreviations: NPI-Q, neuropsychiatric inventory questionnaire; GDS, geriatric depression scale; MMSE, Mini Mental Status Examination; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; BMI, body mass index; NW, normal weight; OW, overweight; OB, obese; MidAge, Middle-Age (<66 years), Senior, seniors (>65 years); yrs, years.

Longitudinal analysis

A total of 634 subjects had both baseline and 2 year behavioral, cognitive and functional data measurements. The mean test scores for all subjects and by BMI are displayed in Table 2. At the 2-year follow-up, average NPS and CDR-SB scores were increased and MMSE scores decreased. The baseline and 2 year ADAS-cog scores significantly differed across BMI groups:

normal weight subjects had higher mean ADAS-cog 13 scores than obese. Normal weight subjects also had a greater degree of cognitive change than obese over two years measured by the ADAS-cog 13, nearly three times the mean change of OB subjects. The CDR-SB change scores were also greatest for NW subjects indicating more cognitive and functional impairments than the OB group. There was no difference in change scores for the NPI-Q, GDS, or the MMSE.

TABLE 3.2. Longitudinal changes in behavior, cognitive and functional test scores over two years for all MCI subjects and across BMI groups

Test	All MCI N = 634	NW	OW	OB	F value	p value
NPI-Q						
Baseline	1.83	1.84	1.67	2.17	1.13	0.326
2 Years	2.53 (.15)	2.40 (.23)	2.43 (.23)	3.01 (.42)	1.13	0.324
Change score	0.71 (.14)	0.55 (.24)	0.79 (.21)	0.84 (.33)	0.40	0.669
GDS						
Baseline	1.69	1.64	1.60	1.97	1.66	0.191
2 Years	1.93	1.86	1.86	2.19	0.12	0.884
Change score	0.30 (.07)	0.28 (.12)	0.31 (.10)	0.33 (.18)	0.03	0.969
MMSE						
Baseline	27.57	27.46	27.57	27.75	1.16	0.314
2 Years	26.36	26.04	26.41	26.78	1.43	0.240
Change score	-1.29 (.12)	-1.44 (.19)	-1.28 (.19)	-1.08 (.26)	0.61	0.543
ADAS-cog 13						
Baseline	16.16 (.27)	16.95 (.45)	16.04 (.38)	15.11 (.62)	3.23	0.040
2 Years	18.63 (.41)	20.48 (.74)	18.29 (.58)	16.36 (.87)	6.95	0.001
Change score	2.46 (.26)	3.52 (.48)	2.21 (.37)	1.25 (.53)	5.33	0.005
CDR - SB						
Baseline	1.54	1.54	1.52	1.56	1.92	0.148
2 Years	2.53	2.74	2.52	2.22	0.12	0.884
Change score	0.99 (.07)	1.19 (.13)	0.99 (.11)	0.66 (.15)	3.29	0.038

Mean comparisons across BMI groups were conducted using an ANOVA model and reported as the mean value and standard deviation. Significance was set at $p < 0.05$.
Abbreviations: 2-yr, 2 year score; NPI-Q, neuropsychiatric inventory questionnaire; GDS, geriatric depression scale; MMSE, Mini Mental Status Examination; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; NW, normal weight; OW, overweight; OB, obese.

Survival analysis

Nine hundred and fifty-six MCI subjects met the inclusion criteria at baseline and were included in the survival analysis. Over 2 years, 172 (27%) subjects converted to probable AD dementia, 23 (3.6%) reverted to normal cognition and 322 (34%) were lost to follow-up. Kaplan Meier plots display the cumulative survival of MCI subjects over 2 years. The survival distribution of our primary factors of interest, BMI (NW, OW, OB), NPS (high/low NPI-Q and GDS) and age (Middle-Aged, Senior) were analyzed first. A log rank test was used to determine if there were differences in the overall survival distributions for the BMI, NPI-Q, GDS and age groups. In the analyses, the cumulative survival did not fall below 50% for any comparisons; therefore median survival estimates were not generated. However, a similar percentage of censorship was present across all group, seen by in the NW (75%), OW (79%), and OB (83%) BMI groups, as well as in the middle age (84%) and Senior (77%) groups. The survival distributions by BMI (Figure 3.1) were not significantly different, X^2 (2) = 4.81, p = 0.090. The high and low NPS symptom group survival distributions also did not differ for the NPI-Q (X^2 (2) = 0.93, p = 0.336) and GDS (X^2 (2) = 0.21, p = 0.64). However, the survival distributions by age group (Figure 3.2) were significantly different between Middle Age and Senior subjects, X^2 (1) = 4.86, p = 0.027. The mean time to conversion was 22 months (95% CI, 21.7 to 22.4) in Senior MCI subjects compared to 23 months (95% CI, 22.0 to 23.2 months) for Middle-aged subjects.

After analyzing the primary factors we then tested the interactions of age with BMI and NPS. The log rank test for the survival distribution factored by age and adjusted for BMI was statistically significant, X^2 (1) = 4.05, p = 0.044 (Figure 3.3). However, further post hoc analysis using pairwise comparisons of age distributions within BMI groups was not able to determine the where the differences were: NW, X^2 (1) = 2.81, p = 0.094, OW, X^2 (1) = 0.706, p = 0.401, OB X^2

(1) = 1.08, p = 0.298. This is likely due to the conservative nature of the test when correcting for multiple comparisons.

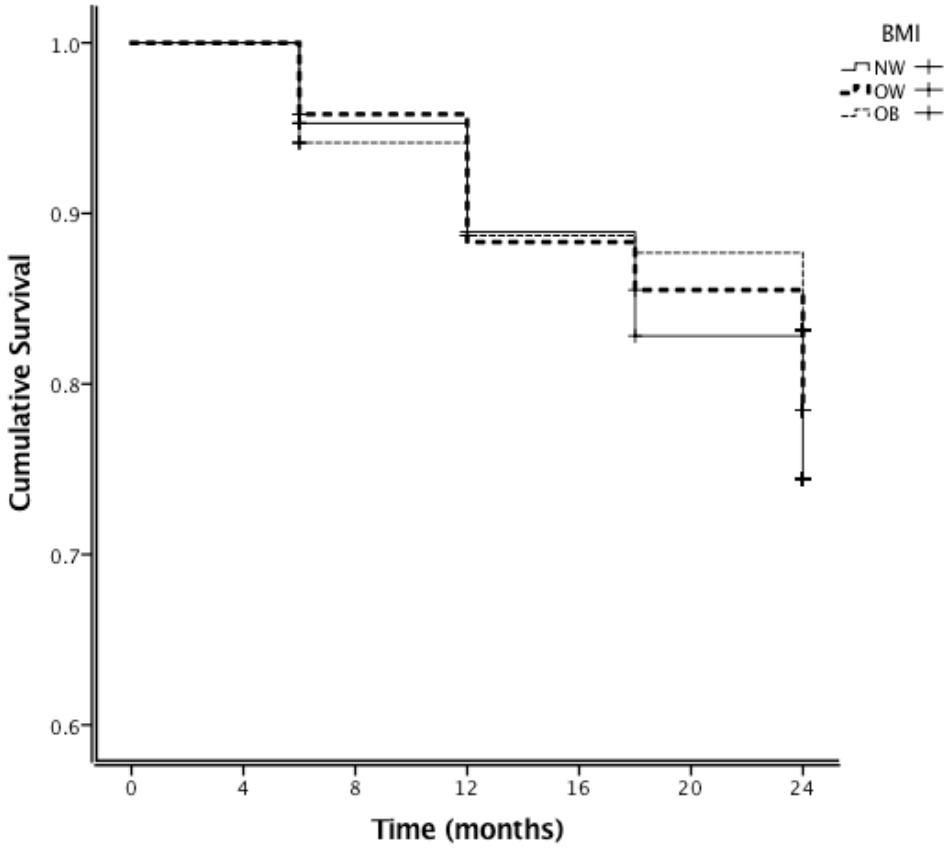

FIGURE 3.1. Kaplan-Meier curves comparing the rate of survival of BMI groups from baseline MCI status to the diagnosis of Alzheimer's type dementia. The cumulative survival of three BMI groups were compared over 24 months or 4 study visits. Crosses indicate censored events. Abbreviations: NW, normal weight; OW, overweight; OB, obese.

Finally, we were interested in the interaction of BMI and age with behavioral scoring on the NPIQ and GDS. Since there was no difference in survival by BMI, the NPS test scores, grouped as high or low, were stratified across age groups (Figure 3.4). These interactions demonstrated an overall significant relationship between age group, and NPI-Q and GDS high/low symptom groups. The survival distributions for Middle-age and Senior groups that had low NPIQ score compared to high NPIQ scores at baseline significantly differed, X^2 (1) = 4.66, p

= 0.031 (Fig. 3.4A). There was also a significant difference in survival distributions for Middle-Age and Seniors that had low GDS score compared to high GDS scores at baseline, X^2 (1) = 4.68, p = 0.031 (Fig. 3.4B). Pairwise comparisons of the low and high NPI-Q groups indicated a significant difference in survival for MCI subjects with low baseline NPI-Q scores, X^2 (1) = 5.0, p = 0.025, indicating a faster progression to AD for Seniors with Low NPI-Q scores at baseline. The difference in survival was not significant for MCI subjects with high baseline NPIQ scores after correction, X^2 (1) = 0.427, p = 0.514. For GDS groups, there was also no difference in the survival distribution for baseline low, X^2 (1) = 3.29, p = 0.070, or high, X^2 (1) = 1.52, p = 0.218, scores after correcting for multiple comparisons.

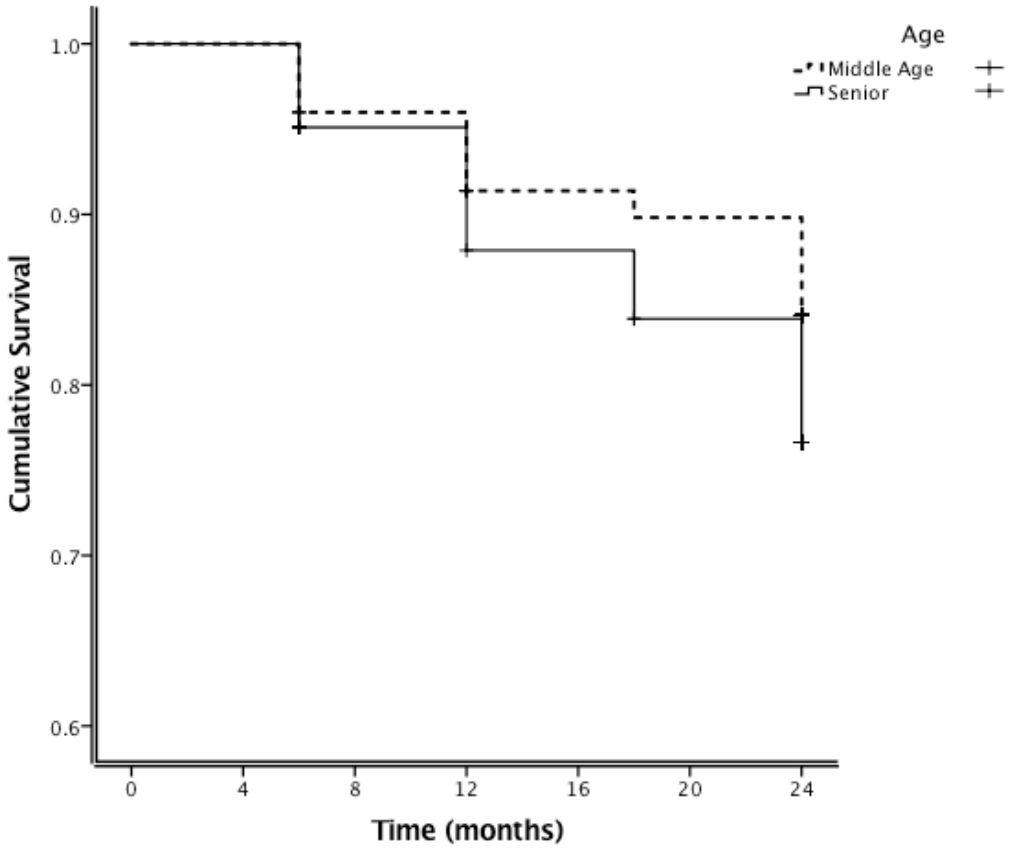

FIGURE 3.2. Kaplan-Meier curves comparing the rate of survival of age groups from baseline MCI status to the diagnosis of Alzheimer's type dementia. The cumulative survival of Middle Age and Senior groups were compared over 24 months or 4 study visits. Crosses indicate censored events.

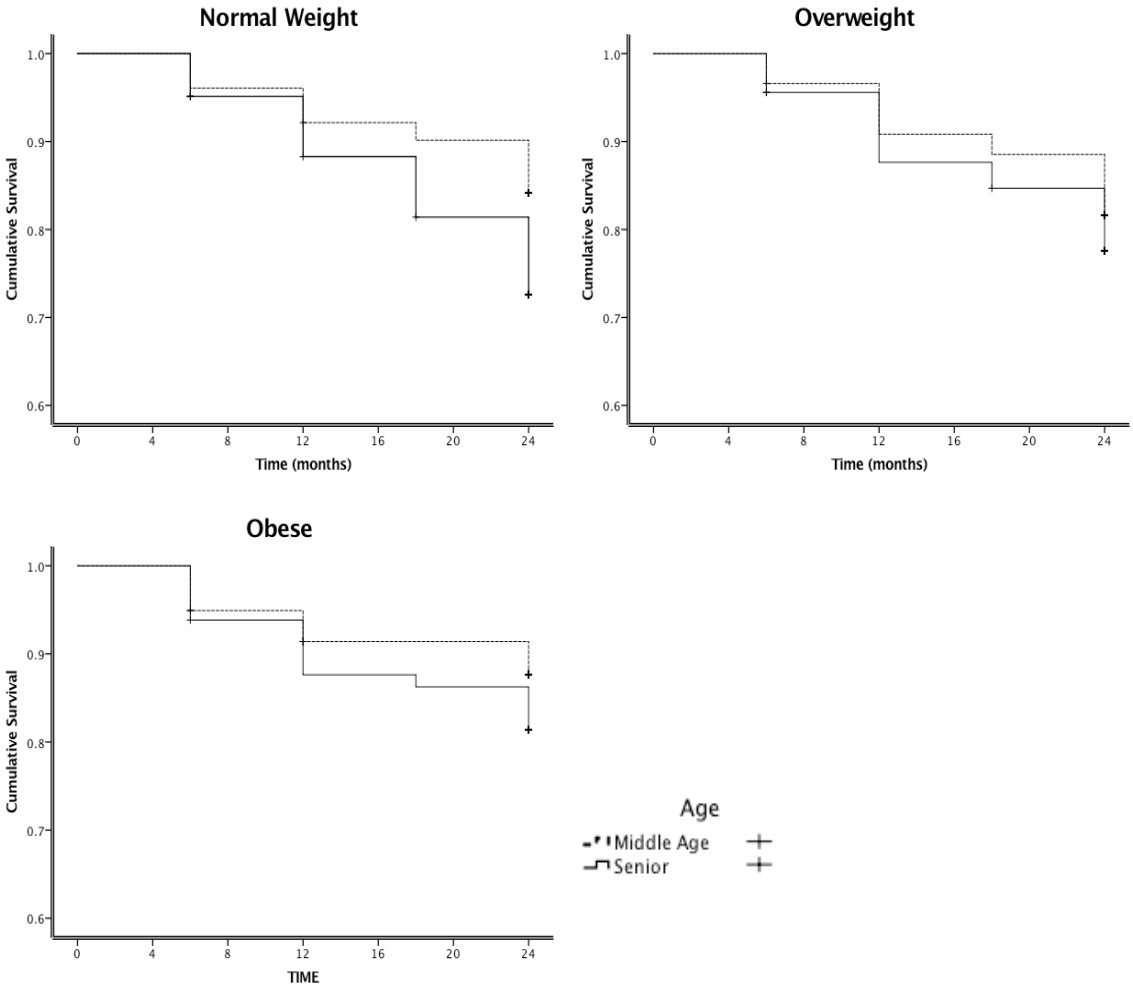

FIGURE 3.3. Kaplan-Meier curves comparing the rate of survival of BMI groups factored by age group from baseline MCI status to the diagnosis of Alzheimer's type dementia. The cumulative survival of Middle Age and Senior subjects within three BMI groups of normal weight, overweight and obese were compared over 24 months or 4 study visits. Crosses indicate censored events.

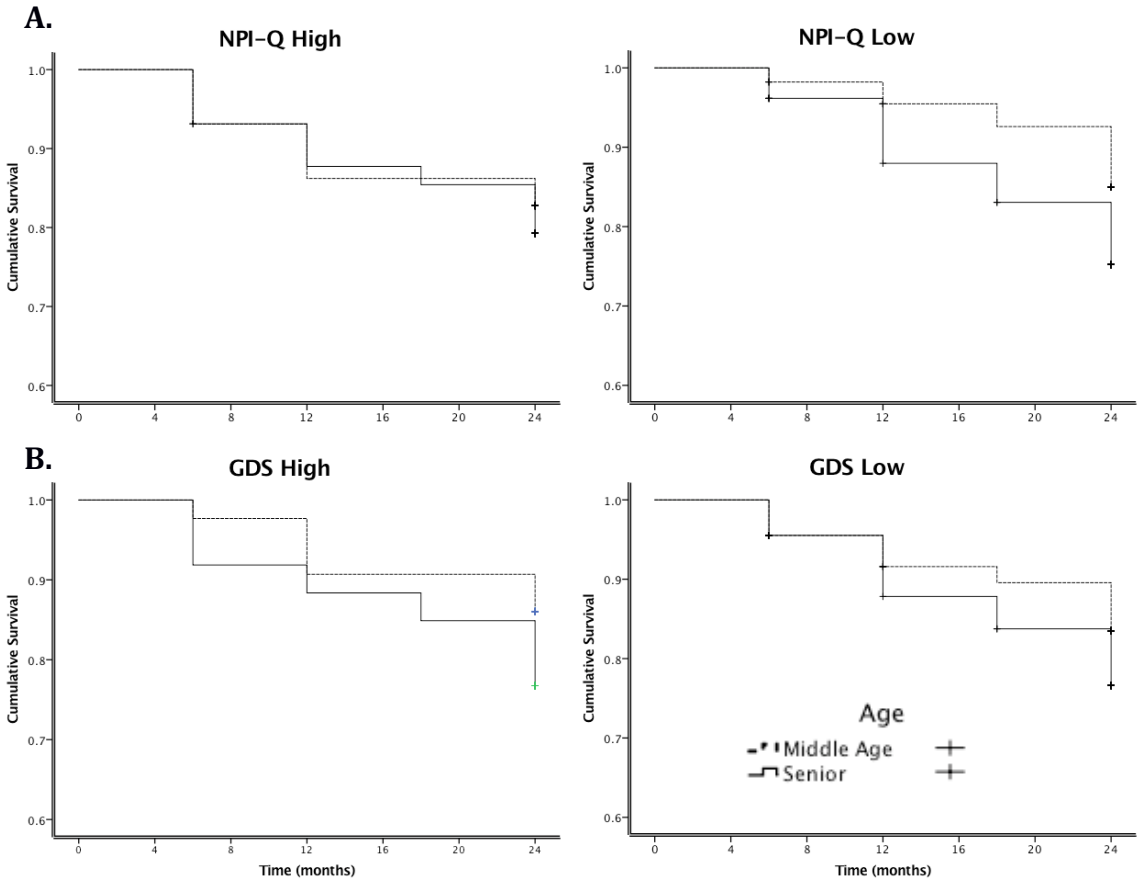

FIGURE 3.4. Kaplan-Meier curves comparing the rate of survival of age groups factored by high and low NPS groups from baseline MCI status to the diagnosis of Alzheimer's type dementia. (A) NPI-Q groups of high and low symptom burden compare the cumulative survival of Middle Age and Senior MCI subjects. (B) GDS groups of high and low symptom burden compare the cumulative survival of Middle Age and Senior MCI subjects. The low group represents total test scores between 0 and 3 and the high scores are ≥ 4. The cumulative survival of age factored by NPS group were compared over 24 months or 4 study visits. Crosses indicate censored events. Abbreviations: NPS, neuropsychiatric symptoms; NPI-Q, Neuropsychiatric Inventory Questionnaire; GDS, Geriatric Depression Scale.

Discussion

This study of over 600 MCI subjects investigated how weight and age influenced the progression of MCI by investigating its cognitive, functional, and behavioral features over two years. We found that NW subjects had greater cognitive changes over 2 years, similar to previous reports[169,176,177,182]. The Kaplan-Meier curves for BMI did not reach significance to show a difference in survival but our sample did show significant, if small, differences in survival based on age group. New findings include the interaction of BMI and age resulting in a change in the survival distribution. Further, the interaction of age and NPS also affected survival in MCI subjects. We were not able to support our hypothesis that middle aged OB have a faster progression time to AD. In our sample, OB individuals had less education, higher NPS scores and multiple metabolic co-morbidities, but equivalent levels of cognitive impairment compared to NW subjects at baseline. We showed that in MCI, a higher proportion of Middle Age subjects were obese compared to Seniors. However, the duration of our study period did not allow for the identification of longitudinal effects of obesity in middle age subjects.

Interestingly, MCI subjects with 4 or more symptoms on the NPI-Q had higher CDR-SB scores (Appendices, Table 3C.) The mean BMI of the NPI-Q high group was significantly higher than the low group, and a higher proportion of OB subject had symptoms ≥ 4. While NW subjects had a lower NPS burden compared to OB they had greater cognitive deficits at each visit (ADAS-cog 13) and in their overall cognitive change score (ADAS-cog 13 and CDR-SB). A possible explanation could be that metabolic and or pathologic changes specific to low body weight MCI subjects are added to by even a low NPS, affecting cognition. Other studies have found that even a mild NPS burden produces significant cognitive changes over time[99,183]. Moreover the younger age of obese subjects may have a protective effect on cognition.

Senior MCI subjects with low NPS at baseline had a decreased time of progression to dementia compared to middle age subjects. The NPI-Q and GDS are common measures of behavioral disturbance in geriatric populations, providing insight into changes in mood and behavior while being easy and quick to administer. Previous work has shown that even one symptom on the NPI-Q can predict future changes in cognitive status. Our average scores for the NPI-Q and GDS were low overall and the difference between groups was in the range of 1 point. While these values are low as far as indicating significant behavioral disturbances, the difference between groups provides evidence for a possible increased risk of dementia to Senior MCI subjects when at least one NPS is present.

Limitations

While this study included a large number of MCI subjects, some limitations should be taken into account. First, the age groups within our sample were unequal with over 3 times the number of Seniors compared to middle aged subjects. A more diverse group in regards to race, ethnicity and educational attainment may provide further insight into how BMI and age influence the progression from MCI to AD over 2 years. Second, the sample was primarily Caucasian and well educated having an average of almost 16 years of education. A wider range of demographic factors may allow for the analysis of patient sub-groups not seen in this study, such as the survival distributions of obese subjects with only a high school education. Third, our Kaplan-Meier analyses did not reach a cumulative survival of at least 50 percent to allow for traditional reporting of median difference. Extending the follow-up time of the analysis may provide for a more sensitive measurement of the survival distributions.

Conclusions

Mild Cognitive Impairment includes a heterogeneous group of individuals and therefore requires the assessment of multiple risk factors for their contributions to disease progression. In this study, we provide insight into how age and weight interact with each other and NPS symptoms to lower the survival of Senior NW individuals. This study is the first of its kind to assess age effects on disease progression within the ADNI cohort, with a focus on middle-aged MCI subjects. Weight and NPS are modifiable risk factors for Alzheimer's type dementia and their relationship with age may indicate groups at highest risk for the conversion to dementia. Further, a targeted approach to recruiting more middle-aged subjects with MCI may provide greater insight to the cognitive, functional and behavioral changes over time specific to this group. Future studies may add to these findings by assessing BMI groups over a longer time period. Further, assessing brain structure changes related to BMI and age after two years may provide additional insight into cognitive changes and overall progression rate to dementia.

APPENDIX

APPENDIX

TABLE 3A. Demographic, cognitive, cardiovascular, and behavioral characteristics comparing Middle-Age and Senior MCI subjects

Characteristic	Middle Age (n = 199)	Senior (n = 756)	Statistic t or X^2	p value
Female, n (%)	104 (52.3)	292 (38.6%)	12.07	0.001
Education, years	16.25 (2.6)	15.85 (2.86)	3.13	0.077
MMSE	28.09 (1.68)	27.43 (1.78)	22.07	< 0.001
CDR sum of boxes	1.51 (0.93)	1.55 (0.89)	0.261	0.609
BMI (kg/m^2)	28.19 (5.41)	26.76 (4.46)	14.84	< 0.001
NW, n (%)	51 (25.8%)	267 (35.4)	6.29	0.012
OW, n (%)	88 (44.4%)	341 (45.2)	0.011	0.918
OB, n (%)	59 (29.8%)	146 (19.4)	10.11	0.001
MAP	94.94 (10.69)	95.35 (10.18)	0.257	0.612
T2D	23 (11.9%)	72 (9.8%)	0.67	0.413
HTN	87 (44.8%)	369 (50.5%)	1.95	0.16
HLP	68 (35.1%)	352 (48.2%)	10.62	0.001
OSA	24 (12.4%)	70 (9.6%)	1.31	0.25
NPI-Q score	2.42 (3.39)	2.23 (3.08)	0.48	0.49
≥ 1	98 (65.8%)	396 (61.9%)	0.78	0.376
≥ 4	37 (24.8%)	146 (22.8%)	0.28	0.6
GDS score	2.07 (1.66)	1.59 (1.49)	15.49	< 0.001
≥ 1	169 (85.4%)	560 (74.1%)	11.08	0.001
≥ 4	42 (21.2%)	86 (11.4%)	13.07	< 0.001

Values are presented as mean (SD) for continuous variables and n (%) for categorical variables. The statistic is chi-square test of independence for categorical variables and a t statistic for continuous variables. Behavioral tests are reported as the mean score and two total symptom categories. The samples for behavioral tests differed for the NPI-Q (n = 789) and GDS (n = 954). Significance was set as $p < 0.05$.

Abbreviations: MCI, Mild Cognitive Impairment; BMI, body mass index; MCI SV, MCI severity; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; CDR, clinical dementia rating scale; NPI-Q, Neuropsychiatric Inventory Questionnaire; NW, normal weight; OW, overweight; OB, obese; MAP, mean arterial pressure; T2D, type-2-diabetes; HTN, hypertension; HLP, hyperlipidemia; OSA, obstructive sleep apnea.

TABLE 3B. Demographic, cognitive, cardiovascular, and behavioral characteristics comparing male and female MCI subjects

Characteristic	Male (n = 559)	Female (n = 396)	Statistic F or X^2	p value
Age, years	73.33 (7.68)	71.34 (7.95)	15.17	< 0.001
Middle Age, n (%)	95 (17%)	104 (26.3%)	12.07	0.001
Senior, n (%)	464 (83%)	292 (73.7%)	12.07	0.001
Education, years	16.26 (2.79)	15.48 (2.78)	18.11	< 0.001
MMSE	27.49 (1.77)	27.68 (1.79)	2.5	0.114
CDR sum of boxes	1.56 (0.9)	1.51 (0.87)	0.58	0.445
BMI (kg/m^2)	27.33 (4.07)	26.67 (5.46)	4.46	< 0.001[a]
NW, n (%)	155 (27.9%)	161 (40.8%)	17.27	< 0.001
OW, n (%)	287 (51.6%)	144 (36.4%)	21.72	< 0.001
OB, n (%)	115 (20.7%)	90 (22.7%)	0.57	0.45
MAP	95.54 (10.11%)	94.88 (10.53%)	0.95	0.33
T2D	65 (12%)	30 (7.8%)	4.3	0.038
HTN	278 (51.4%)	178 (46.4%)	2.28	0.13
HLP	263 (48.6%)	157 (40.9%)	5.41	0.02
OSA	69 (12.8%)	25 (6.5%)	9.59	0.002
NPI-Q score	2.45 (3.3)	1.99 (2.87)	4.18	0.041[a]
≥ 1	299 (64%)	195 (60.6)	0.98	0.32
≥ 4	117 (25.1%)	66 (20.5%)	2.22	0.14
GDS score	1.6 (1.51)	1.82 (1.57)	4.48	0.034
≥ 1	425 (76%)	304 (77%)	0.11	0.74
≥ 4	63 (11.3%)	65 (16.5%)	5.36	0.021

Values are presented as mean (SD) for continuous variables and n (%) for categorical variables. The statistic is chi-square test of independence for categorical variables and a t statistic for continuous variables. Behavioral tests are reported as the mean score and two total symptom categories. The samples for behavioral tests differed for the NPI-Q (n = 789) and GDS (n = 954). Significance was set as $p < 0.05$.

Abbreviations: MCI, Mild Cognitive Impairment; BMI, body mass index; MCI SV, MCI severity; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; CDR, clinical dementia rating scale; NPI-Q, Neuropsychiatric Inventory Questionnaire; NW, normal weight; OW, overweight; OB, obese; MAP, mean arterial pressure; T2D, type-2-diabetes; HTN, hypertension; HLP, hyperlipidemia; OSA, obstructive sleep apnea.

[a] Non-parametric Mann Whitney U test p-value

TABLE 3C. Demographic, cognitive, cardiovascular, and behavioral characteristics comparing MCI subjects with low and high NPI-Q scores

Characteristic	NPI-Q low (n = 606)	NPI-Q high (n = 183)	Statistic t or X^2	p value
Age	73.29 (7.75)	71.66 (7.43)	2.52	0.012
Middle Age, < 66, n (%)	112 (18.5%)	37 (20.2%)	0.277	0.599
Senior, > 66, n (%)	494 (81.5%)	146 (79.8%)	0.277	0.599
Female, n (%)	256 (42.2%)	66 (36.1%)	2.22	0.136
Education	15.93 (2.89)	15.98 (2.7)	0.206	0.831
MMSE	27.56 (1.82)	27.54 (1.77)	0.142	0.887
CDR sum of boxes	1.41 (0.81)	1.9 (0.96)	7.68	<0.001
BMI (kg/m^2)	26.75 (4.53)	27.76 (5.09)	2.57	0.01
NW	215 (35.5%)	52 (28.6%)	3.028	0.082
OW	276 (45.5%)	83 (45.6%)	0.12	0.989
OB	115 (19%)	47 (25.8%)	4.018	0.045
MAP	95.1 (10.3)	95.2 (11.09)	0.118	0.906
T2D	50 (8.4%)	22 (12.4%)	2.59	0.107
HTN	292 (49.2%)	90 (50.8%)	0.156	0.693
HLP	268 (45.1%)	82 (46.3%)	0.081	0.777
OSA	56 (9.4%)	21 (11.9%)	0.901	0.343
GDS score	1.54 (1.37)	2.12 (1.54)	4.55	<0.001
≥ 1	454 (75%)	155 (85.2%)	8.19	0.004
≥ 4	64 (10.6%)	37 (20.3%)	11.89	0.001

Values are presented as mean (SD) for continuous variables and n (%) for categorical variables. The statistic is chi-square test of independence for categorical variables and a t statistic for continuous variables. Behavioral tests are reported as the mean score and two total symptom categories. The samples for behavioral tests differed for the NPI-Q (n = 789) and GDS (n = 954). Significance was set as $p < 0.05$.

Abbreviations: MCI, Mild Cognitive Impairment; BMI, body mass index; MCI SV, MCI severity; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; CDR, clinical dementia rating scale; NPI-Q, Neuropsychiatric Inventory Questionnaire; NW, normal weight; OW, overweight; OB, obese; MAP, mean arterial pressure; T2D, type-2-diabetes; HTN, hypertension; HLP, hyperlipidemia; OSA, obstructive sleep apnea.

TABLE 3D. Demographic, cognitive, cardiovascular, and behavioral characteristics comparing MCI subjects with low and high GDS scores

Characteristic	GDS low (n = 827)	GDS high (n = 126)	Statistic t or X^2	p value
Age, yrs	72.81 (7.73)	70.6 (8.34)	2.96	0.003
Mid Age, n (%)	156 (19%)	41 (32.5%)	12.47	<0.001
Senior, n (%)	670 (81%)	85 (67.5%)	12.21	<0.001
Female, n (%)	330 (40%)	65 (51.6%)	6.10	0.014
Education, yrs	15.94 (2.81)	15.93 (2.82)	0.04	0.971
MMSE	27.58 (1.78)	27.51 (1.77)	0.43	0.665
CDR-SB	1.53 (0.89)	1.59 (0.90)	0.64	0.526
BMI (kg/m^2)	26.93 (4.59)	27.86 (5.38)	1.85	0.67
NW, n (%)	277 (33.7%)	38 (30.2%)	0.60	0.437
OW, n (%)	381 (46.2%)	50 (39.7%)	1.90	0.169
OB, n (%)	166 (20.1%)	38 (30.2%)	6.50	0.011
MAP	95.12 (10.2)	96.15 (10.96)	1.04	0.30
T2D	79 (9.9%)	15 (12.2%)	0.62	0.431
HTN	401 (50.2%)	55 (44.7%)	1.28	0.258
HLP	365 (45.7%)	55 (44.7%)	0.04	0.841
OSA	82 (10.3%)	11 (8.9%)	0.21	0.651
NPI-Q score	2.05 (2.85)	3.67 (4.46)	3.55	0.001
≥ 1	420 (61.2%)	72 (71.3%)	3.80	0.051
≥ 4	145 (21.1%)	37 (36.6%)	11.89	0.001

Values are presented as mean (SD) for continuous variables and n (%) for categorical variables. The statistic is chi-square test of independence for categorical variables and a t statistic for continuous variables. Behavioral tests are reported as the mean score and two total symptom categories. The samples for behavioral tests differed for the NPI-Q (n = 789) and GDS (n = 954). Significance was set as $p < 0.05$.

Abbreviations: MCI, Mild Cognitive Impairment; BMI, body mass index; MCI SV, MCI severity; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; CDR-SB, clinical dementia rating scale- sum of boxes; NPI-Q, Neuropsychiatric Inventory Questionnaire; NW, normal weight; OW, overweight; OB, obese; MAP, mean arterial pressure; T2D, type-2-diabetes; HTN, hypertension; HLP, hyperlipidemia; OSA, obstructive sleep apnea.

CHAPTER 4

ALTERNATE METHODS

THE EFFECT OF OBESITY ON BRAIN WHITE MATTER IN MILD COGNITIVE IMPAIRMENT

Introduction

Changes in white matter microstructure result in altered brain connectivity[184]. A MRI diffusion-weighted imaging sequence quantifies possible changes in axonal integrity via measures of diffusion rate and directionality. When brain white matter is intact, water diffuses along an axon in one direction. However, when there is damage diffusion is altered, suggesting a loss in the myelin sheath that insulates the axon and helps propagate neural impulses. The most commonly used measures include fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AxD). These measures provide estimates of the microstructural integrity of the axon bundles that structurally connect brain regions[185]. Fractional anisotropy is an estimate of fiber integrity reflecting the coherence of the orientation of water diffusion independent of the rate of diffusion, whereas MD, RD, and AxD measure the rate of diffusion along an axis. Mean diffusivity measures the average rate of diffusion; RD measures diffusion perpendicular to the major axis of water diffusion and AxD is the rate of diffusion along the major axis. Each measure is thought to assess different components of white matter structure: MD may increase with decreasing myelination, RD decreases with diminished myelin integrity and AxD may decrease with axonal damage.

Brain white matter is susceptible to microstructural changes associated with MCI and obesity[30,83,186]. Research studies of MCI subjects have demonstrated decreased FA in limbic white matter[24] with values decreasing from normal cognition to MCI to AD. Another study found that diffusivity measures do a better job of distinguishing groups of NC, MCI and AD compared to FA[184]. These studies suggest that as AD pathology progresses clinically, axonal fiber integrity diminishes. Since MCI is an intermediate stage, early changes in white matter

structure are evident and identifying additional factors that influence axonal integrity may highlight features of early pathological changes.

Studies investigating the relationship of weight and brain white matter across a wide age range of adults demonstrate an inverse relationship between BMI and FA values. In limbic system tracts with connections to the temporal and frontal lobe, FA decreases as BMI increases[83,187]. A recent study measuring the association of BMI with all 4 DTI-based measures (FA, MD, AxD, RD) found a negative association with FA and RD in the right middle cerebellar peduncle, and MD and AxD in the bilateral corticospinal tract and anterior thalamic radiation. In the same study, BMI was also positively associated with MD and AxD in the right superior longitudinal fasciculus[186]. As BMI increased so did MD and AxD values suggesting decreased fiber integrity (MD). To date there have not been any studies that investigate the relationship of brain white matter structure and BMI in MCI. The hypothesis for the following experiments is that in MCI, obese subjects will have lower mean FA values and higher MD values indicating deficits in axonal fiber structure and myelination.

There is limited information regarding white matter integrity in obese individuals and none in MCI. The following sections will outline two studies that investigated whether differences in brain white matter existed between BMI groups of MCI subjects. The first study uses a single site research dataset from the MSU Cognitive and Geriatric Neurology Team (COGENT) and the second uses subjects from a large multi-site database, the Alzheimer's disease neuroimaging initiative (ADNI). The methods and results for each study are reported independently with a summary and conclusion on the effect of obesity on MCI brain white matter at the end.

Methods – MSU COGENT

Participants

Nineteen participants (16 MCI and 3 cognitively normal) were recruited from the MSU Neurology clinic and through community advertisements between 2012 - 2014. Participants were diagnosed with MCI based on Petersen criteria[1,5] by an expert neurologist prior to study participation. Inclusion criteria were as follows; subjects were between the ages of 50-95, able to speak, comprehend and read English with at least 8 years of education, and a Mini Mental Status Examination (MMSE) [27] score between 24 - 30. Subjects were excluded from the study if they had a history of a coexisting central nervous system disorder or uncontrolled depression that could account for the cognitive impairment, any uncontrolled or unstable medical condition, and alcohol or substance abuse within the last two years. Exclusion criteria were determined based on medical records review.

Data collection overview

Informed consent was obtained directly from each subject. Subjects were then screened to confirm eligibility (see above inclusion/exclusion criteria), and then underwent magnetic resonance imaging (MRI) scanning followed by neuropsychological and behavioral testing. All study procedures were reviewed and approved by the MSU Institutional Review Board.

MRI acquisition of COGENT data

MRI whole-brain imaging procedures were conducted on a GE 3T Signa HDx MR scanner (GE Healthcare, Waukesha, WI) equipped with an 8-channel head coil in the Radiology Department of MSU. The MRI protocol lasted approximately 40 minutes. During scanning sessions patients were asked to lie still with their eyes open. First and higher-order shimming procedures were carried out to improve magnetic field homogeneity. The scanning procedure included three MRI sequences: resting state fMRI, DTI, and 3D magnetization-prepared rapid

acquisition gradient echo (MPRAGE). The resting state-fMRI data collection involved a 7-minute functional scan with the following parameters: 38 contiguous 3-mm axial slices in an interleaved order, time of echo (TE) = 27.7 ms, time of repetition (TR) = 2500 ms, flip angle = 80^{o}; field of view (FOV) = 22 cm x 22cm, matrix size = 64 x 64, ramp sampling with the first four data points discarded. The first four data points were excluded from analysis due to enhanced longitudinal magnetization in the first few scans. Each volume of slices was acquired 164 times. Next, diffusion-weighted images were acquired using a dual spin-echo echo-planar imaging sequence for 12 minutes and 6 seconds with the following parameters: 48 contiguous 2.4-mm axial slices in an interleaved order, FOV =22cm x 22cm, matrix size=128 x 128, number of excitation (NEX) = 2, echo time (TE) = 77.5 ms, repetition time (TR) = 13.7 s, 25 diffusion-weighted volumes (one per gradient direction) with b=1000 s/mm^2, one volume with b = 0, and parallel imaging acceleration factor = 2. Finally, 180 T-1 weighted 1-mm^3 isotropic volumetric inversion recovery fast spoiled gradient-recalled images were acquired (10 minute scan time). The whole brain was covered with the following parameters: TE=3.8 ms, TR of acquisition =8.6ms, time of inversion (T1) = 831ms, TR of inversion 2332ms, flip angle=8°, FOV =25.6 cm×25.6 cm, matrix size=256 × 256, slice thickness =1 mm, and receiver bandwidth= ± 20.8 kHz.

DTI analyses

DTI data were manually preprocessed using the basic processing steam for FSL (the FMRIB Software Library)[188] . MR images from the scanner were converted from dicom to nifti format, for registration and brain extraction followed by eddy- current distortion and motion correction. Finally, DTIFIT was run to generate diffusion weighted maps, including the FA map. The tract based spatial statistics (TBSS) program was run after DTIFIT in FSL to compute group level statistics of FA (procedure outlined below).

Analyses of DTI images were done in two parts after all images were pre-processed. The first included the analysis of newly recruited MCI subjects (n=12) with a 25-direction DTI sequence. Imaging data from MCI subjects previously collected in our lab with a 25-direction DTI scan (n = 6) were added to the sample for a total group of 18 subjects. The second included the analysis of 19 MCI subjects whose data was previously collected within the COGENT lab and used a 6-diffusion-weighted direction DTI sequence (methods outline below). The two groups were analyzed separately due to differences in the average eigenvalues computed when using 6 compared to 25 directions; the accuracy of estimation may improve at a voxel level as diffusion directions increase,[189] therefore the two groups were not combined . Subjects who met the inclusion criteria and had BMI data were included in the following analyses of white matter tract integrity using TBSS.

MRI acquisition in 6 diffusion weighted directions

MCI subjects previously collected were analyzed using the methods of Bozoki et al 2012. Briefly, scan time was shorter at 4 minutes and 50 sec with 40 axial slices collected using a spin echo EPI pulse sequence with TE = 69.3 ms and TR = 10,000ms. The in-plane resolution = 3 mm, slick thickness = 3mm, interslice gap = 0 mm, 240 mm FOV (80 x 80 matrix), and NEX = 4. For this study the diffusion encoding was collected in six non-collinear directions with b-value of 1,000 s mm^{-2}. DTI images were interpolated on the scanner to a voxel size of 0.9375 x 0.9375 x $3mm^3$.

Tract Based Spatial Statistics (TBSS)

Technique adapted from Smith et al 2006. Voxel-wise statistics were performed by tract-based spatial statistics (TBSS, version 1.2)[190], a part of the FSL program[188]. All subjects' FA data were first aligned into a common space using the FMRIB's nonlinear image registration tool (FNIRT), which uses a b-spline representation of the registration warp field[191]. We then

registered the FA images to the JHU-DTI atlas as a common space in order to correspond the results from voxel wise and ROI analyses. Next, the mean FA image was created and thinned to generate a mean FA skeleton that represents the centers of all tracts common to all subjects. Each subject's aligned FA data was projected onto this skeleton and the resulting data were fed into voxel wise and ROI-based cross-subject statistics. ROI analysis that is limited to the TBSS skeleton was performed using the deep WM atlas (ICBM-DTI-81 white-matter atlas) developed by the Johns Hopkins University (JHU)[192]. Mean values of a diffusion metric for selected ROI segmentations were extracted from each participant.

BMI groups

For this analysis we used MCI subjects with available BMI data. Between groups t-tests were used to compare FA values between a combined normal weight/over-weight group (NW/OW; BMI < 30) and obese group (OB; BMI ≥ 30).

Statistical analysis

Voxel wise statistics were performed by general linear model, a part of the FSL-randomise program. Diffusion metrics (FA) were compared between groups in the TBSS program. Threshold-free cluster enhancement corrected for multiple comparisons with 5,000 permutations. These corrected maps were further thresholded by $P<0.05$. Twenty-six white matter tracts were assessed voxel by voxel as surviving multiple comparisons and P-value thresholding on the WM skeletons. The final statistics included thresholding the mean_FA skeleton, performing a t-test between groups followed by permutation testing (500 times) and test fully corrected for multiple comparisons across time.

Results – MSU COGENT

DTI measures were compared across BMI groups to assess whether the structural integrity of brain white matter differed between groups. After processing the two groups (25-direction and 6-direction sequences) through the TBSS processing stream independently, the mean FA skeletons showed no significant differences between the NW/OW (n = 9) and OB (n = 9) groups. The raw (unthresholded) and multiple correction images for FA in both the 25 and 6-direction scans were non-significant (25 direction, Figure 4.1).

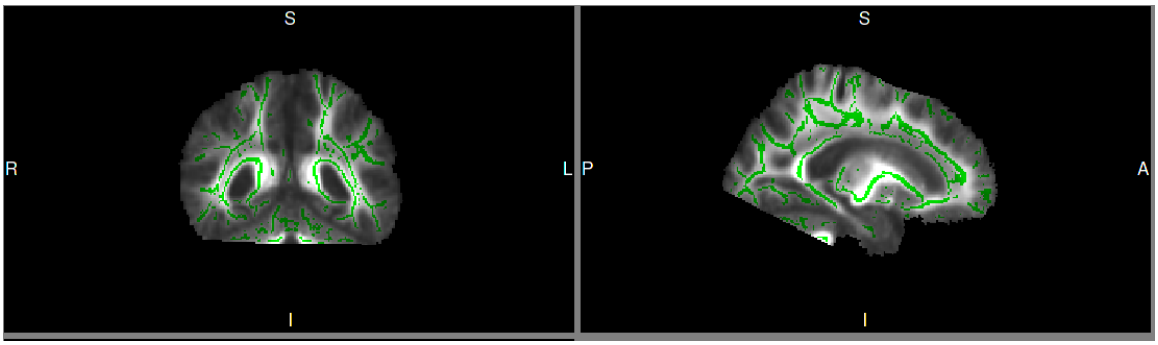

FIGURE 4.1. The 25-direction MSU-COGENT FA results comparing NW/OW and OB groups. Multiple corrections were computed per voxel and overlaid on the mean FA skeleton. The green trace indicates the mean FA comparison between groups and is non-significant shown in a coronal section on the left and a sagittal section on the right. Abbreviations: S, superior; R, right; L, left; I, inferior.

METHODS - ADNI

Participants

MRI data were obtained from the ADNI database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

ADNI subjects were recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these protocols have recruited over 1500 adults ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. Clinical, behavioral and neuroimaging data are collected for each patient with up to 54 months of follow up per patient. MRI methods, procedures and preprocessing by ADNI have been previously described[140] and can also be accessed at the following website: afni-info.org

Inclusion criteria for MCI set forth by ADNI, include; a MMSE score between 24 – 30, a subjective memory complaint by the patient or caregiver, objective memory loss measured by the Wechsler Memory Scale Logical Memory II, a global Clinical Dementia Rating (CDR) of 0.5, preserved activities of daily living, and the absence of dementia.

MRI acquisition of ADNI data

The MRI acquisition of ADNI data has been previously described (Chapter 2-Methods). In brief, all subjects underwent whole-brain MRI scanning on 3-Tesla GE Medical Systems scanner, on at least one of two occasions (baseline and 6 months). T1-weighted IR-FSPGR (spoiled gradient echo) sequences (256×256 matrix; voxel size = 1.2×1.0×1.0 mm^3; TI=400 ms; TR = 6.98 ms; TE = 2.85 ms; flip angle = 11°), were collected as well as diffusion-weighted images (DWI; 35 cm field of view, 128×128 acquired matrix, reconstructed to a 256×256 matrix; voxel size: 2.7×2.7×2.7 mm3; scan time = 9 min; more imaging details may be found at, http://adni.loni.usc.edu/wp-content/uploads/2010/05/ADNI2_GE_3T_22.0_T2.pdf. Forty-six separate images were acquired for each DTI scan: 5 T2-weighted images with no dedicated diffusion sensitization (b0 images) and 41 diffusion-weighted images (b=1000 s/mm^2).
DTI and inversion-recovery spoiled gradient recalled (IR-SPGR) T1-weighted imaging data were acquired on several General Electric 3 T scanners using scanner specific protocols. Briefly, DTI data were acquired with a voxel size of 1.372 × 2.70 mm3, 41 diffusion gradients and a b-value of 1000 s/mm2. In order to increase data uniformity, the data underwent a standardized preprocessing procedure at the ADNI project. All imaging protocols and preprocessing procedures are available at the ADNI website (http://adni.loni.usc.edu/methods/)

DTI analyses

FSL and TBSS procedures were the same as stated above [COGNENT-DTI analyses]. The same JHU 'EVE' atlas was used to calculate FA and MD measures across the 26 DTI tracts. These analyses were done by the Laboratory of Neuro Imaging at USC and made available on the ADNI research website. The DTI-template, with corresponding white matter tract atlas, was registered to each individual subject using the JHU 'EVE' DTI atlas[192], which included a total of

26 regions and 5 summary regions. Summary measures of each tract were computed based off of a subject's mean FA skeleton.

Statistical analysis

To determine whether BMI affected brain connectivity we examined differences in DTI measures across BMI groups. We categorized subjects BMI into three groups of, normal weight (NW, BMI: <25 kg/m^2), overweight (OW, BMI: 25 – 29.9 kg/m^2) and obese (OB, BMI: > 30 kg/m^2). White matter tracts from the JHU 'EVE' DTI atlas[192], a total of 26, were averaged between hemispheres. An analysis of variance (ANOVA) model was used in each experiment to compare the summary ROI measures (FA, MD) of white matter tracts across BMI groups, corrected for age and gender. Statistical significance was set at $p<0.05$. Statistical analyses were performed using SPSS 22.0 (SPSS inc., Chicago, IL).

Results - ADNI

MCI subjects with a MRI diffusion sequence at screening (available in ADNI-GO and ADNI-2 only) totaled 102. We measured the effect of BMI on DTI measures of anisotropy (FA) and diffusivity (MD) in all 26 white matter tracts using an ANOVA model. A large percentage of the sample were overweight (49%) and obese (24.5%). Results indicated differences in BMI in 5 out of 26 tracts for FA, and 4 out of 26 for MD. (Table 4.1.). For each of these regions FA values were lower and MD values were higher for NW subjects. This indicates adverse microstructural changes of lower fiber integrity and myelination for NW subjects.

Based on this initial summary analysis we then analyzed group differences using a MANOVA model in order to control for age and gender, two variables that affect white matter structure. First, we measured the main effect of BMI on FA values and found there were no longer significant differences, $F(52, 148) = 1.17$, $p = 0.23$; Wilks'$\Lambda = 0.502$, partial $\eta\ 2 = 0.29$, nor were was there an effect in the full factorial MANOVA model with covariates, $F(52, 144) =$

1.18, p = 0.22; Wilks'Λ = 0.49, partial η 2 = 0.30. There was also not a main effect of BMI on MD values, F (52, 148) = 1.08, p = 0.28; Wilks'Λ = 0.525, partial η 2 = 0.28, nor in the full factorial model, F (52, 144) = 1.10, p = 0.33; Wilks'Λ = 0.512, partial η 2 = 0.28.

TABLE 4.1. White matter tracts that significantly differed across BMI groups for fractional anisotropy and mean diffusivity measures

Tract label	Tract Name	NW	OW	OB	F value	P value
FA						
ICP	Inferior cerebellar peduncle	0.308 (.01)	0.328 (.04)	0.329 (.03)	3.46	0.035
SCP	Superior cerebellar peduncle	0.411 (.03)	0.426 (.02)	0.415 (.03)	3.38	0.038
PTR	Posterior thalamic radiation	0.365 (.04)	0.387 (.03)	0.380 (.04)	3.01	0.054
FX-ST	Fornix (cres) / Stria terminalis	0.254 (.05)	0.277 (.03)	0.279 (.04)	3.03	0.053
TAP	Tapetum	0.253 (.07)	0.299 (.06)	0.286 (.08)	4.24	0.017
MD						
PTR	Posterior thalamic radiation	1.0x10-3 (1.3x10-4)	9.4x10-4 (1.0x10-4)	9.5x10-4 (1.1x10-4)	3.72	0.028
FX_ST	Fornix (cres) / Stria terminalis	1.4x10-3 (3.0x10-4)	1.3x10-3 (2.6x10-4)	1.2x10-3 (2.8x10-4)	3.58	0.032
SCC	Splenium of corpus callosum	1.2x10-3 (1.8x10-4)	1.1x10-3 (1.2x10-4)	1.1x10-3 (1.7x10-4)	3.45	0.036
TAP	Tapetum	1.8x10-3	1.5x10-3	1.5x10-3	3.57	0.032

Mean fractional anisotropy (FA) and mean diffusivity (MD) values that significantly differed in an ANOVA model. Values are presented as mean (standard error). The statistic is an ANOVA F statistic for continuous variables. Significance was set as $p < 0.05$.
Abbreviations: NW, normal weight; OW, overweight; OB, obese.

Summary and conclusions – MSU COGENT & ADNI DTI analysis

We used two different samples to analyze the relationship between BMI and white matter microstructure. First, the MSU COGENT dataset, a single site, small sample of MCI subjects that were recruited from the mid-Michigan area compared white matter microstructure values of FA across two weight groups (NW/OW and OB). In this study the administration of all neuropsychological, behavioral scales, and DTI processing were completed locally. Due to the limitation of a small sample size in the COGENT study, data from the ADNI, a large, multi-site study, was also examined across three BMI weight groups (NW, OW, OB). The DTI pre-processing and TBSS analysis of FA and MD values in this dataset were completed by ADNI investigators and available for download. In both, BMI was used as a grouping variable to compare white matter microstructure.

In our analyses of the samples, we did not find significant differences in white matter structural measures across BMI groups. In the COGENT study, there were no between group differences in the raw and corrected FA values. In the ADNI study, specific white matter tracts showed microstructural changes of decreased FA and increased MD values, in the brain stem, corpus callosum and temporal lobes, but this effect was lost in the MANOVA model that took into account covariates of age and gender. The initial differences in ADNI all indicated poorer white matter structural integrity for NW MCI subjects. This was similar to our brain volume results (Chapter 2) on regional gray matter volumes.

In older adults with normal cognition, DTI studies indicate an opposite relationship than we found, regarding white matter integrity and weight[83,85,186]. Mild cognitive impairment specific white matter changes included the posterior cingulate cortex and hippocampus[193] while obesity prominently effects the midbrain and brain stem nuclei[194]. A possible explanation for our findings of white matter measures being negatively altered in NW subjects may be that these

subjects are more vulnerable to neural changes associated with their age and likely underlying AD pathology. Fractional anisotropy measures of the fornix and corpus callosum are altered in OB subjects, and their changes in NW may indicate that these regions are related in some way to body weight independent of MCI. Interestingly, our volumetric results (Chapter 2.) indicated decreased volume of the amygdala and hippocampus, which make connections with the fornix and stria terminalis. Further, the tapetum, a bundle of axons branching off the corpus callosum laterally toward the inferior temporal lobe, correspond with the decreased volume in the banks of superior temporal sulcus and inferior middle temporal gyrus also seen in NW subjects. White matter changes of these tracts may suggest early microstructural changes that precede decreases in brain volume and eventual cognitive dysfunction as the severity of MCI progresses over time.

Some limitations may be responsible for the null findings of these analyses. First, the sample size of the MSU COGENT dataset was very small which likely affected the ability to measure differences between even two groups. The ADNI sample was larger with 102 subjects but this analysis was still underpowered to measure differences across three BMI groups. In our ADNI analysis of brain volume across BMI groups we had over 600 subjects and were able to show a medium effect of BMI (partial $\eta 2 = 0.08$) on brain volume. Second, the ADNI data in this study were processed by another lab, not manually computed from the original DTI images. Because of this, the statistics could not be computed within the TBSS procedure thus preventing group level statistics to be drawn directly from the group mean FA and MD skeletons. With the knowledge of differences in brain volume, with regard to BMI group, hypotheses can be generated that outline a targeted approach for understanding the effects of weight on brain white matter a priori, that expand on these analyses and measure changes prospectively. Third, BMI is not the most accurate measure of adiposity and may not definitively establish groups that reflect the true metabolic effects of adiposity on the brain. A study of MCI subjects that uses waist

circumference measures or calculates body fat percentages for each participant may provide a more accurate measure of over-weight and obesity status. Moreover, co-morbid metabolic conditions, such as type 2 diabetes mellitus, hypertension, and serum inflammation markers, must also be taken into account to assess their influence on brain structure compared to BMI alone. Many metabolic conditions are associated with specific white matter changes such as lesions and white matter hyperintensities[195,196]. Finally, utilizing weight groups with cut-offs in values that do not border each other may demonstrate more clearly the differences in brain structure related to adiposity. Overall, increasing the sample sizes of these groups and manually processing the DTI scans may offer a more sensitive approach.

Modern neuroimaging allows us to visualize disease pathology in vivo. In MCI, there may be altered brain structure related to adiposity that affects both neuronal cell bodies and impulse transmission via axon bundles. It is not possible to determine a direction of change: whether white matter damage results in grey matter atrophy or vice-versa. Further investigation into white matter changes of these tracts in MCI subjects is necessary in both normal and over-weight to determine what types of microstructural changes occur that may precede decreases in brain volume and eventual cognitive dysfunction as the severity of MCI progresses over time.

THE EFFECT OF OBESITY ON BRAIN CORTICAL THICKNESS IN MILD COGNITIVE IMPAIRMENT

Introduction

Cortical thickness in neuroimaging is measured as the space between the pial surface and the beginning of brain white matter. The thickness of the cortex is mostly determined genetically but changes throughout life can occur as a result of diseases[197,198]. In MCI, cortical thinning present in frontal brain regions can reliably differentiate progressive compared to stable MCI subjects over time[199]. This can even be more reliable than cognitive test scores. In obese young and older adults with normal cognition, decreased cortical thickness is also evident compared to normal weight adults[137]. Some studies suggest that cortical thinning precedes changes in volume, making cortical thickness measurement a possible early indicator of pathologic influences.

Cortical thickness changes related to obesity are located in specific brain regions. One study found that a high BMI and visceral adipose tissue were independently connected to reduced levels of cortical thickness within the lateral occipital area, inferior temporal lobule, the precentral gyrus and the inferior parietal brain region[200]. Hassenstab et al. examined the cortical thickness of the cognitive control network (CCN, described further in Introduction – Neuroimaging of Obesity) between three groups; successful weight loss maintainers (SWLM), never obese lean (NOL), and obese (OB) individuals. They found that SWLM had a thicker cortex compared to OB and more prefrontal and temporal brain activation when shown pictures of foods high in calories. Obese individuals also had cortical thinning within the anterior cingulate and posterior parietal cortices. They found structural differences within CCN regions between OB and NOLs, yet these regions in SWLM did not significantly differ from the OB group [75,201]. These findings suggest cortical changes are plastic in regards to obesity. The brain

may even alter its structure in relation to positive metabolic changes, or in this case attaining a healthier body weight.

Currently, no studies have investigated cortical thickness changes related to obesity in MCI. Based on previous finding on cortical changes related to obesity and thickness described above, we hypothesized that OB MCI subjects will have decreased cortical thickness averages compared to normal weight (NW) and overweight (OW) groups. This study focused primarily on region directly related to either MCI or obesity and included 17 regions from the frontal, parietal and temporal lobes. The full list of regions is located in Table 4B.

Methods

Participants

The analysis for this project began in 2015 with the collection of ADNI MCI subject data that met the inclusion criteria for MCI with a baseline MRI scan and FreeSurfer analysis. The study procedures, MCI inclusion criteria and MRI acquisition protocol are documented in Chapter 4 [MRI acquisition of ADNI data], and FreeSurfer analysis methods are found in Chapter 2 [ADNI FreeSurfer methods].

Cortical thickness analysis

Alzheimer's disease neuroimaging initiative MCI subjects with a screening MRI scan and FreeSurfer analysis were included in the data analysis of cortical thickness measurements across BMI groups. All three phases of ADNI were used and merged into one dataset. Subjects with a non-accelerated T1 image, that passed the 'Overall QC' a quality check for accurate cortical parcellation by FreeSurfer of the frontal, parietal, occipital and temporal lobes were included in this study. From this sample, demographic (age, sex, BMI), cognitive (MMSE) and behavioral (NPI-Q and GDS) measures were then matched to each MCI subject. A total of 76 brain regions

were included in the FreeSurfer analysis, from this list we selected regions previously identified as related to obesity. The left and right hemisphere data was combined for each region, resulting in a total of 17 regions. These regions were analyzed preliminarily to our cortical volume measures within chapter 2. The few papers that highlight cortical thickness changes related to weight, showed significant changes in these specific regions and the full list is available in Table 4B.

FreeSurfer region of interest analysis

The ROI thickness average (TA) values were generated using FreeSurfer and made available on the ADNI website was for download. Data was obtained from the UCSFFX spreadsheet of FreeSurfer Version 5.1. Subjects that had a non-accelerated T1 screening MRI, whose status was complete and had an overall quality check (QC) of Pass for all QC regions were included in the analyses.

Statistical analysis

An ANOVA model was used to compare average thickness measures for each region across BMI groups. First, the main of effect of BMI was calculated across all 17 regions. Then, a full factorial model included age and education as covariates. The analysis was conducted using SPSS version 22. Statistical significance was set at $p < 0.05$.

Results

There were 635 MCI subjects that met the inclusion criteria and had MRI data that passed the overall quality check for FreeSurfer indicating successful cortical parcellation. The demographic, behavioral and cognitive measures across BMI groups were the same as those reported in Table 2.1.

Brain cortical thickness

Baseline cortical thickness averages were compared across BMI groups to determine whether there was a difference in mean thickness related to the subject's BMI. First, a MANOVA model measured the main effect of BMI on regional brain volumes. There was a statistically significant difference in brain thickness averages based on BMI group, $F(34, 1234) = 1.61$, $p = 0.015$; Wilks'$\Lambda = 0.917$, partial $\eta^2 = 0.042$. Next, age and education were added as covariates based on previous research indicating their relationship with the cortical thickness of the brain. In this full factorial model, BMI, and age were independent significant contributors to volume differences in the overall multivariate tests, although education was not: BMI: $F(34,1226) = 1.60$, $p = 0.017$; Wilks'$\Lambda = 0.917$, partial $\eta^2 = 0.042$; Age: $F(17, 613) = 15.171$, $p < .005$; Wilks'$\Lambda = 0.704$, partial $\eta^2 = 0.296$; Education: $F(17, 613) = 1.468$, $p = 0.10$; Wilks'$\Lambda = 0.961$, partial $\eta^2 = 0.039$. In the full factorial model, 3 (out of 17) regions significantly differed by BMI, the Precuneus, lateral occipital cortex and the post central gyrus. Table 4.2 shows the brain regions that differed in cortical thickness measures across BMI groups. For all significant comparisons cortical thickness was lower in NW subjects compared to OW and/or OB.

TABLE 4.2. Brain regions that significantly differed in cortical thickness average measures across BMI groups of MCI subjects

Brain Region	NW	OW	OB	F	p value
Precuneus	2.11 (0.18)	2.17 (0.19)	2.21 (0.19)	7.36	0.001[a,b]
Lateral Occipital Cortex	2.03 (0.18)	2.08 (0.17)	2.10 (0.17)	5.06	0.007[a,b]
Post Central gyrus	1.82 (0.16)	1.86 (0.17)	1.87 (0.15)	3.11	0.045[b]

Values are reported as the mean (standard deviation (SD)). The MANOVA model corrected for age and education. Superscripts indicate the direction of the differences after Bonferroni method correction: a = NW < OB, b = NW < OW. Statistical significance is set at $p < 0.05$.
Abbreviations: NW, normal weight; OW, overweight; OB, obese.

Summary and conclusions – Thickness averages

In this sub-study of ADNI FreeSurfer data, we sought to identify whether BMI was related to decreased cortical thickness in MCI subjects. The available data on the effect of weight on cortical thickness measures is limited and has not been studied in MCI. We again combined the 3 phases of ADNI and found small yet significant effects of BMI on cortical thickness in a MANOVA model that included age and educations covariates. In our analysis, NW subjects had significantly lower cortical thickness measurements in 3 out of 17 brain regions compared to OW and OB subjects

In our study, only two regions overlapped with the volume reductions we saw in NW subjects, the precuneus and the lateral occipital cortex. An additional region, the post central gyrus, also had a lower thickness average in NW compared to OB subjects, yet there were no volume differences for this region. To better compare our volumetric and cortical thickness analyses, we also analyzed cortical brain volumes using only the 17 regions within the cortical thickness analyses. The MANOVA model for this comparison showed a significant effect of BMI on brain volumes, $F(34, 1224) = 1.86$, $p = 0.002$; Wilks'$\Lambda = 0.904$, partial $\eta^2 = 0.05$. All of the regions that were significant in the original volume analysis and included in this smaller analysis remained significant; middle temporal gyrus ($F = 5.26$, $p = 0.005$), rostral anterior cingulate gyrus ($F = 4.04$, $p = 0.018$), insula ($F = 3.56$, $p = 0.029$), precuneus ($F = 7.33$, $p = 0.001$), and the lateral occipital gyrus ($F = 4.90$, $p = 0.008$).

Initially, this study was designed to provide a complete assessment on brain structural changes with the hope of complementing the investigation of grey matter volume and white matter microstructure. However, there were not consistent changes in brain regions across our multiple neuroimaging modalities. This inconsistency may be due to the wide range of ages included in our analyses. While reduced cortical thickness has been hypothesized as an early

indicator of cortical change[199] this may only be true when investigating discreet age ranges. A recent study has shown that as a person ages there is a dynamic relationship in the direction and magnitude of changes to cortical thickness, surface area and the total volume of brain regions[197]. For example, this study demonstrated that in adults with normal cognition ranging in age from 23 – 87 years, as age increased there was accelerated changes in temporal and occipital brain regions, while frontal and anterior cingulate regions decelerated in overall volume, surface area and thickness. These finding may help explain why only two regions overlapped between our cortical thickness and cortical volume analyses; due to the significant differences in age across BMI groups (Table 2.1).

Our study had a large age range of over 30 years (age range 55 – 89 years) which may require targeted analysis of Middle-Age and Senior groups as well as investigating discreet age ranges within these two larger age categories. More work needs to be done to better understand the effect obesity has on brain structure in older adults with normal cognition and in those with pathological changes that are a signature of MCI or Alzheimer's disease. Future studies should assess volume and cortical thickness measures together, with a specific focus on measuring the relationship of BMI and brain structure within discreet age groups of MCI subjects.

APPENDIX

APPENDIX

TABLE 4A. Regions of interest from the JHU 'EVE' atlas white matter tract list generated in FreeSurfer

ROI Label	ROI definition
ACR	Anterior corona radiata*
ALIC	Anterior limb of internal capsule *
BCC	Body of corpus callosum *
CGC	Cingulum*
CGH	Cingulum (hippocampus)*
CP	Cerebral peduncle
CST	Corticospinal tract
EC	External capsule*
FX	Fornix *
FX_ST	Fornix (cres) / Stria terminalis*
GCC	Genu of corpus callosum*
ICP	Inferior cerebellar peduncle
IFO	Inferior fronto-occipital fasciculus*
ML	Medial lemniscus
PCR	Posterior corona radiata *
PLIC	Posterior limb of internal capsule*
PTR	Posterior thalamic radiation
RLIC	Retrolenticular part of internal capsule*
SCC	Splenium of corpus callosum*
SCP	Superior cerebellar peduncle
SCR	Superior corona radiate*
SFO	Superior fronto-occipital fasciculus*
SLF	Superior longitudinal fasciculus*
SS	Sagittal stratum*
TAP	Tapetum *
UNC	Uncinate fasciculus*
SUMBCC	Bilateral body of the corpus callosum*
SUMCC	Bilateral full corpus callosum*
SUMFX	Bilateral fornix*
SUMGCC	Bilateral genu of the corpus callosum*
SUMSCC	Bilateral splenium of the corpus callosum*

White matter tract list from the JHU "EVE" atlas. There are a total of 26 unique tracts and 5 summary measures. The ROI label lists the atlas label and the ROI definition indicates the full name of the white matter tract or adjacent brain region. *White matter commissural and association fibers.

TABLE 4B. Selected brain regions of interest for the cortical thickness analysis generated in FreeSurfer

ROI Label	Region Name
Precuneus	Precueus
LateralOccipital	Lateral occipital gyrus
PostCentral	Postcentral gyrus
ParsOrbital	Pars orbitalis
ParOperc	Pars opercularis
ParsTriang	Pars triangularis
ParaHipp	Parahippocampal gyrus
MiddleTemp	Middle temporal gyrus
InfTemporal	Inferior temporal gyrus
ParaCentral	Paracentral gyrus
RostralAntCing	Rostral anterior cingulate gyrus
CaudalAntCing	Caudal anterior cingulate gyrus
Insula	Insular cortex
CaudalMidFront	Caudal middle frontal gyrus
RostralMidFront	Rostral middle frontal gyrus
SuperiorFrontal	Superior frontal gyrus
PreCentral	Precentral gyrus

Seventeen brain regions were selected based on literature that indicated a relationship of the region and structural brain changes related to weight or BMI. The ROI label indicated the FreeSurfer label and the Region Name gives the full anatomical name for each region.

CHAPTER 5

CONCLUSIONS AND FUTURE DIRECTIONS

Prior to this work the intersections of obesity, NPS, age and cognitive decline in MCI had not been explored. This dissertation has begun to explore these relationships. Each of the previously mentioned elements are an independent risk factor for the ultimate development of dementia and may or may not have a significant effect on the time to conversion additively. While we have provided new insight into these relationships more research is necessary. It is not well understood how NPS and obesity structurally and functionally alter the brain in the presence of cognitive deficits, or whether those factors are additive. In addition, the direction of the relationship linking NPS and obesity with AD and with each other is not well understood. And results in more questions such as, does obesity cause a relatively toxic environment to neurons thereby producing brain damage over time, or is obesity a marker for certain pre-existing brain "weaknesses" (e.g. as seen in the cognitive control network) that enable the emergence of cognitive impairment more readily at a later age? We do know that NPS tends to emerge de novo at the time MCI onset, whereas obesity is highly likely to have persisted throughout adolescence, adulthood, middle age and later life. Thus, NPS is more likely to be a marker for emerging brain pathology while obesity is more likely to indicate either a pre-existing or an ongoing state of independent loss of connectivity.

This research has provided new information on the effects of obesity in MCI. First, it was demonstrated that in MCI obese subjects have a higher prevalence of NPS measured by the NPI-Q. Specifically, OB had a higher percentage of affective symptoms of depression and anxiety and when these symptoms were present, they were most severe. In Chapter 1. type-2-diabetes mellitus and obstructive sleep apnea also have specific NPS associated with these conditions. Throughout each of the preceding chapters, when measured, obese subjects had significantly higher mean NPI-Q scores compared to NW subjects. However, we were not able to draw a direct connection between obesity, NPS and deficits in cognition.

Many factors emerged in Chapters 2 – 4 that may influence or mediate the effects of weight on either cognition, or brain structure. The effects of obesity on cognitive decline are demonstrated when OB are middle age. Studies that have shown this relationship sampled individuals with normal cognition. In our studies, we did not see a cross sectional difference in cognitive scoring related to obesity. In our cross-sectional imaging study, we found that normal weight MCI subjects had lower brain volumes and similar cognitive scores as OW and OB subjects. While we expected to see deficits primarily related to obesity Chapters 2 and 3 of this dissertation identified that difference related to BMI were driven by the normal weight group. In Chapter 2, NW subjects had lower brain volumes and in Chapter 3 lower baseline cognitive scores (ADAS-cog) followed by greater cognitive changes over two years. These studies suggest that in regards to increased risk for cognitive decline and progression to dementia, normal weight MCI subjects may be a high-risk group. Despite obese subjects having higher NPS and more metabolic comorbidities, NW subjects were more vulnerable to structural brain changes, which likely preceded the cognitive changes that occurred after two years.

Another well-known factor that we simply grouped was age. This was done to highlight that MCI comprises two very different life stages, an approach that has not been taken in current research. In our samples, the NW group was consistently older than the OB group. The age of NW subjects is likely a large driving factor that plays a role in the expression of dementia related pathologic changes in a way that is more dominate than mood and physiologic changes related to metabolic conditions. So, where does that leave future research on obese MCI subjects? One could argue that the young age of OB subjects should not be overlooked. Even if their clinical course to dementia is slower, the development of MCI at a young age could be related an early development of AD. With a large prevalence of obese MCI subjects this groups needs better characterization in future work, specifically, middle age obese persons with MCI.

The goal of this dissertation was to introduce obesity as a measurable risk factor for Alzheimer's disease within MCI. The ultimate goal of nearly all MCI research involves understanding the development of Alzheimer's disease. Thus, research studies that identify BMI groups in MCI have done so only in cases where progression to Alzheimer's disease is being studied directly, such as longitudinal and survival analysis research. The focus of this research took a new direction, to study and characterize obesity in MCI directly. With the high prevalence of obesity on the rise from adolescences to older adulthood, the effects of chronic obesity on brain and behavior over a lifetime are relatively unknown. The addition of a pathological disorder to the aging process, such as MCI, introduces an avenue where there is no knowledge regarding the effect that increased weight has on the presentation of the disease, or what symptoms reflect metabolic changes and not the disease pathology. In this research, we were not able to take into account some key features that may answer such complex questions regarding the interaction between chronic obesity and Alzheimer's disease pathology. Future directions of this research involve tracking the chronicity of obesity and using that time variable as a control measure for brain structure changes. In addition, designing studies prospectively where changes in BMI are tracked over time, along with cognitive, brain imaging and behavioral measures. Further, many of the studies in this dissertation categorized BMI into three categories of NW, OW and OB, but a study design that uses regression analyses may identify relationships of weight and brain structure that provide interpretations on associative relationship that could change under different conditions.

REFERENCES

REFERENCES

1. Petersen R, Smith G, Waring S, Ivnik R, Tangalos E, Kokmen E. Mild Cognitive Impairment: Clinical Characterization and Outcome. *Arch Neurol*. 1999;56:303-309.

2. Petersen R, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol*. 2001;58(12):1985-1992.

3. Petersen R. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256:183-194.

4. Palmer K, Berger A, Monastero R, Winblad B, Bäckman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology*. 2007;68(19):1596-1602.

5. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment-beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256(3):240-246. doi:10.1111/j.1365-2796.2004.01380.x.

6. Jack C, Petersen R, Xu Y, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 1999;52(7):1397.

7. Leon MJ De, Convit A, Wolf OT, et al. Prediction of cognitive decline in normal elderly subjects with 2- [18 F] fluoro-2-deoxy- D-glucose/ positron-emission tomography (FDG/PET). *PNAS*. 2001;98(19):10966-10971.

8. Hardy J, Selkoe D. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science (80-)*. 2002;297:353-356. doi:10.1126/science.1072994.

9. Crews L, Masliah E. Molecular mechanisms of neurodegeneration in Alzheimer's disease. *Hum Mol Genet*. 2010;19(R1):R12-20. doi:10.1093/hmg/ddq160.

10. Schuff N, Woerner N, Boreta L, et al. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain*. 2009;132(4):1067-1077.

11. Roses A. Apolipoprotein E alleles as risk factors in Alzheimer's disease. *Annu Rev Med*. 1996;47:387-400.

12. Stern Y, Gurland B, Tatemichi T, Tang M, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA*. 1994;271(13):1004-1010.

13. Ott A, Breteler M, van Harskamp F, et al. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. *BMJ*. 1995;310:970-973.

14. Amieva H, Jacqmin-Gadda H, Orgogozo J, et al. The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study. *Brain*. 2005;128(5):1093-1101.

15. Sperling R, Aisen P, Beckett L, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's. *Alzheimer's Dement*. 2011;7(3):280-292. doi:10.1016/j.jalz.2011.03.003.Toward.

16. Bozoki A, Giordani B, Heidebrink J. Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. *Arch Neurol*. 2001;58(3):411-416.

17. Fischer P, Jungwirth S, Zehetmayer S, et al. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology*. 2007;68(4):288-291.

18. McDonald CR, Gharapetian L, McEvoy LK, et al. Relationship between regional atrophy rates and cognitive decline in mild cognitive impairment. *Neurobiol Aging*. 2012;33(2):242-253. doi:10.1016/j.neurobiolaging.2010.03.015.

19. Tartaglia MC, Rosen HJ, Miller BL. Neuroimaging in dementia. *Neurotherapeutics*. 2011;8(1):82-92. doi:10.1007/s13311-010-0012-2.

20. Bruen PD, McGeown WJ, Shanks MF, Venneri A. Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. *Brain*. 2008;131(Pt 9):2455-2463. doi:10.1093/brain/awn151.

21. Duara R, Loewenstein D a, Greig MT, et al. Pre-MCI and MCI: neuropsychological, clinical, and imaging features and progression rates. *Am J Geriatr Psychiatry*. 2011;19(11):951-960. doi:10.1097/JGP.0b013e3182107c69.

22. Petrovic P, Kalso E, Petersson K, Ingvar M. Placebo and opioid analgesia--imaging a shared neuronal network. *Science (80-).* 2002;295:1737-1740.

23. Dickerson BC, Stoub TR, Shah RC, et al. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *Neurology*. 2011;76(16):1395-1402. doi:10.1212/WNL.0b013e3182166e96.

24. Bozoki AC, Korolev IO, Davis NC, Hoisington L a, Berger KL. Disruption of limbic white matter pathways in mild cognitive impairment and Alzheimer's disease: a DTI/FDG-PET study. *Hum Brain Mapp*. 2012;33(8):1792-1802. doi:10.1002/hbm.21320.

25. Steffens DC, McQuoid DR, Payne ME, Potter GG. Change in hippocampal volume on magnetic resonance imaging and cognitive decline among older depressed and nondepressed subjects in the neurocognitive outcomes of depression in the elderly study. *Am J Geriatr psychiatry*. 2011;19(1):4-12. doi:10.1097/JGP.0b013e3181d6c245.

26. Laakso M, Soininen H, Partanen K, et al. Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions. *J Neural Transm*. 1995;9(1):73-86.

27. Folstein M, Folstein S, McHugh P. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.

28. Visser PJ, Verhey FRJ, Hofman PAM, Scheltens P, Jolles J. Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. *J Neurol Neurosurg Psychiatry*. 2002;72:491-497.

29. Delano-Wood L, Bondi MW, Sacco J, et al. Heterogeneity in mild cognitive impairment: differences in neuropsychological profile and associated white matter lesion pathology. *J Int Neuropsychol Soc*. 2009;15(6):906-914. doi:10.1017/S1355617709990257.

30. Delano-Wood L, Abeles N, Sacco JM, Wierenga CE, Horne NR, Bozoki A. Regional white matter pathology in mild cognitive impairment: differential influence of lesion type on neuropsychological functioning. *Stroke*. 2008;39(3):794-799. doi:10.1161/STROKEAHA.107.502534.

31. Zhang Y, Schuff N, Jahng G, et al. Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. *Neurology*. 2007;68(1):13-19.

32. Mosconi L. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. *Eur J Nucl Med Mol Imaging*. 2005;32:486-510. doi:10.1007/s00259-005-1762-7.

33. Mosconi L, Mistur R, Switalski R, et al. FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease. *Eur J Nucl Med Mol Imaging*. 2009;36:811-822. doi:10.1007/s00259-008-1039-z.

34. Wee C, Yap P-T, Denny K, et al. Resting-state multi-spectrum functional connectivity networks for identification of MCI patients. *PLoS One*. 2012;7(5):e37828. doi:10.1371/journal.pone.0037828.

35. Xie C, Bai F, Yu H, et al. Abnormal insula functional network is associated with episodic memory decline in amnestic mild cognitive impairment. *Neuroimage*. 2012;63(1):320-327. doi:10.1016/j.neuroimage.2012.06.062.

36. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci*. 2007;8(9):700-711. doi:10.1038/nrn2201.

37. Alexopoulos GS, Hoptman MJ, Kanellopoulos D, Murphy CF, Lim KO, Gunning FM. Functional connectivity in the cognitive control network and the default mode network in late-life depression. *J Affect Disord*. 2012;139(1):56-65. doi:10.1016/j.jad.2011.12.002.

38. Zhu DCD, Majumdar S, Korolev IIO, Berger KL, Bozoki AC. Alzheimer's Disease and Amnestic Mild Cognitive Impairment Weaken Connections Within the Default-Mode

Network: A Multi-Modal Imaging Study. *J Alzheimer's Dis*. 2013;34(4):969-984. doi:10.3233/JAD-121879.

39. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008;1124:1-38. doi:10.1196/annals.1440.011.

40. Binnewijzend M, Schoonheim MM, Sanz-Arigita E, et al. Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging*. 2012;33(9):2018-2028.

41. Damoiseaux JS, Beckmann CF, Arigita EJS, et al. Reduced resting-state brain activity in the "default network" in normal aging. *Cereb Cortex*. 2008;18(8):1856-1864.

42. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci*. 2011;15(10):483-506.

43. Cole M, Schneider W. The cognitive control network: Integrated cortical regions with dissociable functions. *Neuroimage*. 2007;37(1):343-360.

44. Feldman H, Scheltens P, Scarpini E, et al. Behavioral symptoms in mild cognitive impairment. *Neurology*. 2004;62(7):1199-1201.

45. Lyketsos C, Lopez O. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment. *JAMA*. 2002;288(12):1475-1483.

46. Apostolova LGL, Cummings JLJ. Neuropsychiatric manifestations in mild cognitive impairment: a systematic review of the literature. *Dement Geriatr Cogn Disord*. 2008;25:115-126. doi:10.1159/000112509.

47. Palmer K, di Iulio F, Varsi AE, et al. Neuropsychiatric predictors of progression from amnestic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. *J Alzheimers Dis*. 2010;20(1):175-183. doi:10.3233/JAD-2010-1352.

48. Geda YE, Roberts RO, Knopman DS, et al. The prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: A population-based study. *Arch Gen Psychiatry*. 2008;65(10):1193-1198. doi:10.1001/archpsyc.65.10.1193.

49. Rozzini L, Vicini Chilovi B, Conti M, et al. Neuropsychiatric symptoms in amnestic and nonamnestic mild cognitive impairment. *Dement Geriatr Cogn Disord*. 2008;25:32-36. doi:10.1159/000111133.

50. Teng W, Lu PH, Cummings JL. Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2007;24(4):253-259. doi:10.1159/000107100.

51. Rose S, McMahon K, Janke A, et al. Diffusion indices on magnetic resonance imaging

and neuropsychological performance in amnestic mild cognitive impairment. *J Neurol Neurosurg Psychiatry*. 2006;77:1122-1128.

52. Edwards E, Spira A, Barnes D, Yaffe K. Neuropsychiatric symptoms in mild cognitive impairment: differences by subtype and progression to dementia. *Int J Geriatr Psychiatry*. 2009;24(7):716-722.

53. Lyketsos C, Carrillo M, Ryan J, et al. Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dement*. 2011;7(5):532-539. doi:10.1016/j.jalz.2011.05.2410.Neuropsychiatric.

54. Balthazar M, Pereira F. Neuropsychiatric symptoms in Alzheimer's disease are related to functional connectivity alterations in the salience network. *Hum Brain Mapp*. 2013.

55. Bae JN, MacFall JR, Krishnan KRR, Payne ME, Steffens DC, Taylor WD. Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations in late-life depression. *Biol Psychiatry*. 2006;60(12):1356-1363. doi:10.1016/j.biopsych.2006.03.052.

56. Tighe SK, Oishi K, Mori S, et al. Diffusion Tensor Imaging of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Alzheimer's Dementia. 2012;24(4):484-488. doi:10.1176/appi.neuropsych.11120375.Diffusion.

57. Hettema JJM, Kettenmann B, Ahluwalia V, et al. Pilot multimodal twin imaging study of generalized anxiety disorder. *Depress Anxietynd anxiety*. 2012;29(3):202-209. doi:10.1002/da.20901.

58. Norris CJ, Chen EE, Zhu DC, Small SL, Cacioppo JT. The interaction of social and emotional processes in the brain. *J Cogn Neurosci*. 2004;16(10):1818-1829. doi:10.1162/0898929042947847.

59. Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol*. 2008;24(4):424-430. doi:10.1097/WCO.0b013e328306f2c5.

60. Aalten P, Verhey F, Boziki M, et al. Neuropsychiatric syndromes in dementia. *Dement Geriatr Cogn Disord*. 2007;24:457-463.

61. Ogden CCL, Carroll M, Fryar C, Flegal K. Prevalence of Obesity Among Adults and Youth: United States, 2011-2014. *Med Benefits*. 2015;33(1):5.

62. Must A, Spadano J, Coakley EH, Field A, Colditz G, Dietz W. The Disease Burden Associated With Overweight and Obesity. *JAMA*. 1999;282(16):1523-1529. doi:10.1001/jama.282.16.1523.

63. Han T, Tajar A, Lean M. Obesity and weight management in the elderly. *Br Med Bull*. 2011;97:169-196.

64. Sharma A, Padwal R. Obesity is a sign - over-eating is a symptom: an aetiological

framework for the assessment and management of obesity. *Obes Rev*. 2010;11(5):362-370. doi:10.1111/j.1467-789X.2009.00689.x.

65. Papachristou E, Ramsay SE, Lennon LT, et al. The relationships between body composition characteristics and cognitive functioning in a population-based sample of older British men. *BMC Geriatr*. 2015;15:172. doi:10.1186/s12877-015-0169-y.

66. Gustafson D. Adiposity indices and dementia. *Lancet Neurol*. 2006;5(8):713-720. doi:10.1016/S1474-4422(06)70526-9.

67. Beydoun M, Beydoun H, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes Rev*. 2008;9(3):204-218. doi:10.1111/j.1467-789X.2008.00473.x.

68. Whitmer R, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology*. 2008;71(14):1057-1064. doi:10.1212/01.wnl.0000306313.89165.ef.

69. Hildreth KL, Van Pelt RE, Schwartz RS. Obesity, insulin resistance, and Alzheimer's disease. *Obesity*. 2012;20:1549-1557. doi:10.1038/oby.2012.19.

70. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol*. 2011;29:415-445. doi:10.1146/annurev-immunol-031210-101322.

71. Flier JS. Obesity Wars: Molecular Progress Confronts an Expanding Epidemic. *Cell*. 2004;116:337-350. doi:10.1016/S0092-8674(03)01081-X.

72. Walther K, Birdsill A, Glisky E, Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. *Hum Brain Mapp*. 2010;31(7):1052-1064. doi:10.1002/hbm.20916.

73. Zeki Al Hazzouri A, Stone KL, Haan MN, Yaffe K. Leptin, mild cognitive impairment, and dementia among elderly women. *J Gerontol A Biol Sci Med Sci*. 2013;68(2):175-180. doi:10.1093/gerona/gls155.

74. Castanon N, Lasselin J, Capuron L. Neuropsychiatric comorbidity in obesity: role of inflammatory processes. *Front Endocrinol (Lausanne)*. 2014;5(74):1-9. doi:10.3389/fendo.2014.00074.

75. Hassenstab J, Sweet L, Parigi A, et al. Cortical thickness of the cognitive control network in obesity and successful weight loss maintenance: A preliminary MRI study. *Psychiatry Res Neuroimaging*. 2012;202(1):77-79.

76. Stoeckel L, Kim J, Weller R, Cox J, Cook W, Horwitz B. Effective connectivity of a reward network in obese women. *Brain Res Bull*. 2009;79(6):388-395.

77. Stice E, Spoor S, Bohon C, Veldhuizen M, Small D. Relation of Reward from Food Intake

and Anticipated Food Intake to Obesity: A Functional Magnetic Resonance Imaging Study. *J Abnorm Psychol*. 2008;117(4):924-935. doi:10.1037/a0013600.Relation.

78. Lee N, Carter A, Owen N, Hall W. The neurobiology of overeating. *EMBO Rep*. 2012;13:785-790.

79. Pannacciulli N, Parigi A Del, Chen K, Le D, Reiman E, Tataranni P. Brain abnormalities in human obesity: a voxel-based morphometric study. *Neuroimage*. 2006;31:1419-1425.

80. Raji CA, Ho AJ, Parikshak N, et al. Brain Structure and Obesity. *Hum Brain Mapp*. 2011;31(3):353-364. doi:10.1002/hbm.20870.Brain.

81. Driscoll I, Beydoun M a, An Y, et al. Midlife obesity and trajectories of brain volume changes in older adults. *Hum Brain Mapp*. 2012;33(9):2204-2210. doi:10.1002/hbm.21353.

82. Ho A, Raji C, Becker J, et al. Obesity is linked with lower brain volume in 700 AD and MCI patients. *Neurobiol Aging*. 2010;31(8):1326-1339. doi:10.1016/j.neurobiolaging.2010.04.006.

83. Stanek KKM, Grieve SSM, Brickman AMA, et al. Obesity is associated with reduced white matter integrity in otherwise healthy adults. *Obesity*. 2011;19:500-504. doi:10.1038/oby.2010.312.

84. Marks B, Katz L, Styner M, Smith J. Aerobic fitness and obesity: relationship to cerebral white matter integrity in the brain of active and sedentary older adults. *Br J Sports Med*. 2011;45:1208-1215.

85. Karlsson HHK, Tuulari JJJ, Hirvonen J, et al. Obesity is associated with white matter atrophy: A combined diffusion tensor imaging and voxel-based morphometric study. *Obesity*. 2013;21(12):2530-2537. doi:10.1002/oby.20386.

86. Pelchat M, Johnson A, Chan R, Valdez J, Ragland J. Images of desire: food-craving activation during fMRI. *Neuroimage*. 2004;23:1486-1493.

87. Simon GE, Von Korff M, Saunders K, et al. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry*. 2006;63(7):824-830. doi:10.1001/archpsyc.63.7.824.

88. Allison DB, Newcomer JW, Dunn AL, et al. Obesity among those with mental disorders: a National Institute of Mental Health meeting report. *Am J Prev Med*. 2009;36(4):341-350. doi:10.1016/j.amepre.2008.11.020.

89. Barefoot J, Heitmann B, Helms M, Williams R, Surwit R, Siegler I. Symptoms of depression and changes in body weight from adolescence to mid-life. *Int J Obes*. 1998;22:688-694.

90. Boutelle KKN, Hannan P, Fulkerson JA, Crow SJ, Stice E. Obesity as a prospective predictor of depression in adolescent females. *Heal Psychol*. 2010;29(3):293-298. doi:10.1037/a0018645.

91. Roberts R, Deleger S, Strawbridge W, Kaplan G. Prospective association between obesity and depression: evidence from the Alameda County Study. *Int J Obes*. 2003;27:514-521.

92. Levitan RD, Davis C. Emotions and Eating Behaviour: Implications for the Current Obesity Epidemic. *Univ Toronto Q*. 2010;79(2):783-799. doi:10.3138/utq.79.2.783.

93. Vago DR, Epstein J, Catenaccio E, Stern E. *Identification of Neural Targets for the Treatment of Psychiatric Disorders: The Role of Functional Neuroimaging.* Vol 22.; 2011. doi:10.1016/j.nec.2011.01.003.

94. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res*. 2002;53(2):647-654.

95. Soczynska JK, Kennedy SH, Woldeyohannes HO, et al. Mood disorders and obesity: understanding inflammation as a pathophysiological nexus. *Neuromolecular Med*. 2011;13(2):93-116. doi:10.1007/s12017-010-8140-8.

96. Misiak B, Leszek J, Kiejna A. Metabolic syndrome, mild cognitive impairment and Alzheimer's disease--the emerging role of systemic low-grade inflammation and adiposity. *Brain Res Bull*. 2012;89(3-4):144-149. doi:10.1016/j.brainresbull.2012.08.003.

97. Petersen R, Thomas R, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005;352:1-10.

98. Rogers S, Doody R. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. *Arch Intern Med*. 1998;158(9):1021-1031.

99. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimer's Dement*. 2016;12(2):195-202. doi:10.1016/j.jalz.2015.05.017.

100. Lyketsos C, Lopez O, Jones B, Fitzpatrick A, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA*. 2002;288(12):1475-1483.

101. Zhao Q-F, Tan LL, Wang H-F, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord*. 2016;190:264-271. doi:10.1016/j.jad.2015.09.069.

102. Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. *Am J Geriatr Psychiatry*. 2012;21(7):685-695. doi:10.1016/j.jagp.2013.01.006.

103. Gorska-Ciebiada M, Saryusz-Wolska M, Ciebiada M, Loba J. Mild cognitive impairment and depressive symptoms in elderly patients with diabetes: prevalence, risk factors, and comorbidity. *J Diabetes Res*. 2014;2014:179648. doi:10.1155/2014/179648.

104. Kandimalla R, Thirumala V, Reddy PH. Is Alzheimer's disease a Type 3 Diabetes? A critical appraisal. *Biochim Biophys Acta*. 2016;1863(5):1078-1089. doi:10.1016/j.bbadis.2016.08.018.

105. Flegal KM, Carroll MD, Ogden CL, Curtin LR, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2010;303(3):1723-1727.

106. Moms J, Heyman A, Mohs R, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assesment of Alzheimer's disease. *Neurology*. 1989;39(9):1159.

107. Li J, Wang Y, Zhang M, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology*. 2011;76(17):1485-1491.

108. Steinberg M, Hess K, Corcoran C, et al. Vascular risk factors and neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study. *Int J Geriatr Psychiatry*. 2014;29(2):153-159. doi:10.1002/gps.3980.

109. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12(2):233-239.

110. Herrman N, Mittmann N, Silver IL, et al. A validation study of the Geriatric Depression Scale short form. *Int J Geriatr Psychiatry*. 1996;11:457-460.

111. Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FRJ. The course of neuropsychiatric symptoms in dementia. Part II: relationships among behavioural sub-syndromes and the influence of clinical variables. *Int J Geriatr Psychiatry*. 2005;20(6):531-536. doi:10.1002/gps.1317.

112. Teng E, Chui H. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987;48:314-318.

113. Atkinson R, Shiffrin R. The control of short-term memory. *Sci Am*. 1971;225:82-90.

114. Kaplan E, Goodglass H, Weintraub S. The Boston naming test, 2nd. *Philadelphia Lea Febiger*. 1983.

115. Borkowski J, Benton A, Spreen O. Word fluency and brain damage. *Neuropsychologia*. 1967;5(2):135-140.

116. Tombaugh T. Trail Making Test A and B: Normative data stratified by age and education. *Arch Clin Neuropsychol*. 2004;10(2):203-214.

117. Stroop J. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643-662.

118. Rosen W, Mohs R, Davis K. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356-1364.

119. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of Childhood and Adult Obesity in the United States, 2011-2012. *JAMA*. 2014;311(8):806. doi:10.1001/jama.2014.732.

120. Luppino F, Wit L de, Bouvy P. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67(3):220-229.

121. Katon W, Lyles C, Parker MM, Karter AJ, Huang ES, Whitmer RA. Association of depression with increased risk of dementia in patients with type 2 diabetes: the Diabetes and Aging Study. *Arch Gen Psychiatry*. 2012;69(4):410-417.

122. Akmal MK, Ezat M, Raafat O, Hamed H, Bediwy A. Association of depression, anxiety, and impairment in executive functions in patients with obstructive sleep apnea. *Middle East Curr Psychiatry*. 2013;20(1):30-34. doi:10.1097/01.XME.0000422808.09000.59.

123. Vernet C, Redolfi S, Attali V, et al. Residual sleepiness in obstructive sleep apnoea: Phenotype and related symptoms. *Eur Respir J*. 2011;38(1):98-105. doi:10.1183/09031936.00040410.

124. Sharma S, Fernandes M, Fulton S. Adaptations in brain reward circuitry underlie palatable food cravings and anxiety induced by high-fat diet withdrawal. *Int J Obes*. 2013;37:1183-1191.

125. Gustafson D. A life course of adiposity and dementia. *Eur J Pharmacol*. 2008;585(1):163-175. doi:10.1016/j.ejphar.2008.01.052.

126. Rosenberg PB, Mielke MM, Appleby B, et al. Neuropsychiatric symptoms in MCI subtypes: the importance of executive dysfunction. *Int J Geriatr Psychiatry*. 2012;26(4):364-372. doi:10.1002/gps.2535.Neuropsychiatric.

127. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's disease Neuroimaging Initiative (ADNI) clinical characterization. *Neurology*. 2010;74(3):201-209. doi:10.1212/WNL.0b013e3181cb3e25.

128. Flegal K, Kruszon-Moran D, Carroll M, Fryar C, Ogden C. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016;315(21):2284-2291.

129. Bischof GN, Park DC. Obesity and Aging : Consequences for Cognition, Brain Structure, and Brain Function. *Psychosom Med*. 2015;77:697-709. doi:10.1097/PSY.0000000000000212.

130. Yokum S, Ng J, Stice E. Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. *Int J Obes*. 2011;36(10):656-664. doi:10.1038/ijo.2011.175.

131. Albanese E, Davis B, Jonsson P V, et al. Overweight and Obesity in Midlife and Brain Structure and Dementia 26 Years Later: The AGES-Reykjavik Study. *Am J Epidemiol*. 2015;181(9):672-679. doi:10.1093/aje/kwu331.

132. Smith E, Hay P, Campbell L, Trollor JN. A review of the association between obesity and cognitive function across the lifespan : implications for novel approaches to prevention and treatment. *Obes Rev*. 2011;12:740-755. doi:10.1111/j.1467-789X.2011.00920.x.

133. Elias MF, Goodell AL, Waldstein SR. Obesity, cognitive functioning and dementia: back to the future. *J Alzheimer's Dis*. 2012;30:S113-S125. doi:10.3233/JAD-2011-111175.

134. Whitmer R, Gunderson E, Barrett-Connor E, Quesenberry C, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ*. 2005;330:1360.

135. Banack H, Kaufman J. The "Obesity Paradox" Explained. *Epidemiology*. 2013;24(3):461-462. doi:10.1097/EDE.0b013e31828c776c.

136. Fielding RA, Gunstad J, Gustafson DR, et al. The paradox of overnutrition in aging and cognition. *Ann N Y Acad Sci*. 2013;1287(1):31-43. doi:10.1111/nyas.12138.

137. Marqués-Iturria I, Pueyo R, Garolera M, et al. Frontal cortical thinning and subcortical volume reductions in early adulthood obesity. *Psychiatry Res Neuroimaging*. 2013;214(2):109-115. doi:10.1016/j.pscychresns.2013.06.004.

138. Mueller SG, Weiner MW, Thal LJ, et al. Ways toward an early diagnosis in Alzheimer's disease: The Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimer's Dement*. 2005;1(1):55-66.

139. Jack CCR, Bernstein MA, Fox NC, et al. The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. *J Magn Reson Imaging*. 2008;27(4):685-691. doi:10.1002/jmri.21049.

140. Weiner M, Veitch D, Aisen P, et al. The Alzhiemer's Disease Neuroimaging Initiative: A review of papers published since its inception. *Alzheimer's Dement*. 2012;8(10):S1-68. doi:10.1016/j.jalz.2011.09.172.The.

141. Dale A, Fischl B, Sereno M. Cortical surface-based analysis: I. Segmentation and surface reconstruction. *Neuroimage*. 1999;9:179-194.

142. Dale A, Sereno M. Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a linear approach. *J Cogn Neurosci*. 1993;5:162-176.

143. Fischl B, Dale A. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000;97:11050-11055.

144. Fischl B, Liu A, Dale A. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med Imaging*. 2001;20:70-80.

145. Fischl B, Salat D, Busa E, Albert M, Dieterich M. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002;33:341-355.

146. Fischl B, Salat D, Kouwe A van der, Makris N. Sequence-independent segmentation of magnetic resonance images. *Neuroimage*. 2004;23(Suppl 1):S69-84.

147. Fischl B, Sereno M, Dale A. Cortical surface-based analysis: II: inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999;9:195-207.

148. Fischl B, Sereno M, Tootell R, Dale A. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp*. 1999;8:272-284.

149. Fischl B, van der Kouwe A, Destrieux C. Automatically parcellating the human cerebral cortex. *Cereb Cortex*. 2004;14:11-22.

150. Han X, Jovicich J, Salat D, et al. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. *Neuroimage*. 2006;32:180-194.

151. Jovicich J, Czanner S, Greve D, et al. Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. *Neuroimage*. 2006;30:436-443.

152. Ségonne F, Dale A, Busa E, et al. A hybrid approach to the skull stripping problem in MRI. *Neuroimage*. 2004;22:1060-1075.

153. Reuter M, Rosas H, Fischl B. Highly accurate inverse consistent registration: a robust approach. *Neuroimage*. 2010;53:1181-1196.

154. Reuter M, Schmansky N, Rosas H, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage*. 2012;61(4):1402-1418.

155. Sled J, Zijdenbos A, Evans A. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging*. 1998;17:87-97.

156. Ségonne F, Pacheco J, Fischl B. Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Trans Med Imaging*. 2007;26:518-529.

157. Desikan R, Ségonne F, Fischl B, Quinn B. An automated labeling system for subdividing

the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31:968-980.

158. Rosas H, Liu A, Hersch S, et al. Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology*. 2002;58:695-701.

159. Kuperberg G, Broome M, McGuire P, et al. Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry*. 2003;60:878-888.

160. Salat D, Buckner R, Snyder A, Greve D. Thinning of the cerebral cortex in aging. *Cereb Cortex*. 2004;14:721-730.

161. Kharabian Masouleh S, Arélin K, Horstmann A, et al. Higher body mass index in older adults is associated with lower gray matter volume: Implications for memory performance. *Neurobiol Aging*. 2016;40:1-10. doi:10.1016/j.neurobiolaging.2015.12.020.

162. Boyle CP, Raji CA, Erickson KI, et al. Physical activity, body mass index, and brain atrophy in Alzheimer's disease. *Neurobiol Aging*. 2015;36(1):S194-202. doi:10.1016/j.neurobiolaging.2014.05.036.

163. Miller AA, Spencer SJ. Obesity and neuroinflammation: A pathway to cognitive impairment. *Brain Behav Immun*. 2014;42:10-21. doi:10.1016/j.bbi.2014.04.001.

164. Xu W, Caracciolo B, Wang H-X, et al. Accelerated Progression From Mild Cognitive Impairment to Dementia in People With Diabetes. *Diabetes*. 2010;59(11):2928-2935. doi:10.2337/db10-0539.

165. Lupien SJ, de Leon M, de Santi S, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci*. 1998;1(1):69-73. doi:10.1038/271.

166. Catani M, de Schotten MT. *Atlas of Human Brain Connections*. 1st ed. Oxford University Press; 2012.

167. Fitzpatrick A, Kuller L, Lopez O, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol*. 2009;66(3):336-342. doi:10.1001/archneurol.2008.582.Mid-.

168. Doruk H, Naharci MI, Bozoglu E, Isik a. T, Kilic S. The relationship between body mass index and incidental mild cognitive impairment, Alzheimer's disease, and Vascular Dementia in elderly. *J Nutr Health Aging*. 2010;14(10):834-838. doi:10.1007/s12603-010-0113-y.

169. Sobów T, Fendler W, Magierski R. Body mass index and mild cognitive impairment-to-dementia progression in 24 months: a prospective study. *Eur J Clin Nutr*. 2014;68(11):1216-1219. doi:10.1038/ejcn.2014.167.

170. Tolppanen AM, Ngandu T, Kåreholt I, et al. Midlife and late-life body mass index and late-life dementia: Results from a prospective population-based cohort. *J Alzheimer's Dis*. 2014;38(1):201-209. doi:10.3233/JAD-130698.

171. Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by statistical analysis. *Gastroenterol Hepatol Bed Bench*. 2012;5(2):79-83.

172. Savva G, Wharton S, Ince P, Forster G, Matthews F, Brayne C. Age, Neuropathology, and Dementia. *N Engl J Med*. 2009;360(22):2302-2309.

173. Hryhorczuk C, Sharma S, Fulton S. Metabolic disturbances connecting obesity and depression. *Front Neurosci*. 2013;7:177.

174. David N, Lin F, Porsteinsson A. Trajectories of neuropsychiatric symptoms and cognitive decline in mild cognitive impairment. *Am J Geriatr Psychiatry*. 2015;24(1):70-80. doi:10.1016/j.jagp.2015.06.001.

175. Hsu CL, Voss MW, Best J, et al. Elevated body mass index and maintenance of cognitive function in late life: Exploring underlying neural mechanisms. *Front Aging Neurosci*. 2015;7(JUL):1-14. doi:10.3389/fnagi.2015.00155.

176. Cronk B, Johnson D, Burns J. Body Mass Index and Cognitive Decline in Mild Cognitive Impairment. *Alzheimer Dis Assoc Disord*. 2010;24(2):126-130. doi:10.1097/WAD.0b013e3181a6bf3f.Body.

177. Cova I, Clerici F, Maggiore L, et al. Body Mass Index Predicts Progression of Mild Cognitive Impairment to Dementia. *Dement Geriatr Cogn Disord*. 2016;41(3-4):172-180. doi:10.1159/000444216.

178. Alhurani RE, Vassilaki M, Aakre JA, et al. Decline in Weight and Incident Mild Cognitive Impairment. *JAMA Neurol*. 2016;73(4):439. doi:10.1001/jamaneurol.2015.4756.

179. Cova I, Clerici F, Rossi A, et al. Weight loss predicts progression of mild cognitive impairment to Alzheimer's disease. *PLoS One*. 2016;11(3):e0151710. doi:10.1371/journal.pone.0151710.

180. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140(6):566-572. doi:10.1192/BJP.140.6.566.

181. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457-481. doi:10.2307/2281868.

182. Ye BS, Jang EY, Kim SY, et al. Unstable Body Mass Index and Progression to Probable Alzheimer's Disease Dementia in Patients with Amnestic Mild Cognitive Impairment. *J Alzheimer's Dis*. 2015;49(2):1-9. doi:10.3233/JAD-150556.

183. Pietrzak RH, Maruff P, Woodward M, et al. Mild Worry Symptoms Predict Decline in Learning and Memory in Healthy Older Adults: A 2-Year Prospective Cohort Study. *Am J Geriatr Psychiatry*. 2012;20(3):266-275. doi:10.1097/JGP.0b013e3182107e24.

184. Nir TM, Jahanshad N, Villalon-Reina JE, et al. Effectiveness of regional DTI measures in distinguishing Alzheimer's disease, MCI, and normal aging. *NeuroImage Clin*. 2013;3:180-195. doi:10.1016/j.nicl.2013.07.006.

185. Charlton R, Schiavone F, Barrick T, Morris R, Markus H. Diffusion tensor imaging detects age related white matter change over a 2 year follow-up which is associated with working memory decline. *J Neurol Neurosurg Psychiatry*. 2010;81(1):13-19. doi:10.1136/jnnp.2008.167288.

186. Kullmann S, Callaghan MF, Heni M, et al. Specific white matter tissue microstructure changes associated with obesity. *Neuroimage*. 2016;125:36-44. doi:10.1016/j.neuroimage.2015.10.006.

187. Kullmann S, Schweizer F, Veit R, Fritsche a, Preissl H. Compromised white matter integrity in obesity. *Obes Rev*. 2015;16(4):273-281. doi:10.1111/obr.12248.

188. Smith S, Jenkinson M, Woolrich M, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004;23:S208-S219.

189. Ni H, Kavcic V, Zhu T, Ekholm S, Zhong J. Effects of number of diffusion gradient directions on derived diffusion tensor imaging indices in human brain. *Am J Neuroradiol*. 2006;27(8):1776-1781. doi:27/8/1776 [pii].

190. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage*. 2006;31(4):1487-1505. doi:10.1016/j.neuroimage.2006.02.024.

191. Rueckert D, Sonoda LI, Hayes C, Hill DLG, Leach MO, Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging*. 1999;18(8):712-721. doi:10.1109/42.796284.

192. Mori S, Oishi K, Jiang H, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage*. 2008;40(2):570-582. doi:10.1016/j.neuroimage.2007.12.035.

193. Zhou Y, Dougherty J, Hubner K, Bai B, Cannon R, Hutson R. Abnormal connectivity in the posterior cingulate and hippocampus in early Alzheimer's disease and mild cognitive impairment. *Alzheimer's Dement*. 2008;4(4):265-270.

194. Papageorgiou I, Astrakas LG, Xydis V, et al. Abnormalities of brain neural circuits related to obesity : A Diffusion Tensor Imaging study. *Magn Reson Imaging*. 2017;37:116-121. doi:10.1016/j.mri.2016.11.018.

195. Moran C, Phan TG, Chen J, et al. Brain atrophy in type 2 diabetes: regional distribution and influence on cognition. *Diabetes Care*. 2013;36(12):4036-4042. doi:10.2337/dc13-0143.

196. van Bloemendaal L, Ijzerman RG, ten Kulve JS, et al. Alterations in white matter volume and integrity in obesity and type 2 diabetes. *Metab Brain Dis*. 2016;31(3):621-629. doi:10.1007/s11011-016-9792-3.

197. Storsve AB, Fjell AM, Tamnes CK, et al. Differential Longitudinal Changes in Cortical Thickness, Surface Area and Volume across the Adult Life Span: Regions of Accelerating and Decelerating Change. *J Neurosci*. 2014;34(25):8488-8498. doi:10.1523/JNEUROSCI.0391-14.2014.

198. Brundel M, Kappelle LJ, Biessels GJ. Brain imaging in type 2 diabetes. *Eur Neuropsychopharmacol*. 2014;24(12):1967-1981. doi:10.1016/j.euroneuro.2014.01.023.

199. Querbes O, Aubry F, Pariente J, et al. Early diagnosis of Alzheimer's disease using cortical thickness: impact of cognitive reserve. *Brain*. 2009;132(8):2036-2047. doi:10.1093/brain/awp105.

200. Veit R, Kullmann S, Heni M, et al. Reduced cortical thickness associated with visceral fat and BMI. *NeuroImage Clin*. 2014;6:307-311. doi:10.1016/j.nicl.2014.09.013.

201. Sweet L, Hassenstab J, McCaffery J, et al. Brain response to food stimulation in obese, normal weight, and successful weight loss maintainers. *Obesity*. 2012;20(11):2220-2225.