

OBESITY AND PHYSICAL FUNCTIONING: ASSOCIATIONS WITH COGNITION
IN THE ADVANCED COGNITIVE TRAINING FOR INDEPENDENT AND VITAL
ELDERLY (ACTIVE) COHORT

by

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Abstract

The current study reviewed mechanisms through which obesity influences cognitive performance as well as explored the dynamic relationship between body weight, physical performance, and cognition in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial over a 10-year period.

Findings from the study highlight the complex relationship between physical health and cognitive performance in older adults and suggest that higher body mass index (BMI) at baseline was associated with both cognitive and functional performance. Results from Aim 1 suggest that better performance on multiple cognitive domains was associated with attenuated declines in BMI over 10 years. Furthermore, attenuated cognitive declines were associated with a greater increase in BMI.

Analyses from Aim 2 explored the mediated effect of grip-strength on weight-related changes in BMI. Findings revealed that a higher BMI at baseline was associated with better grip strength at baseline and accelerated declines in grip strength over time; whereas higher grip strength at baseline was associated with slower declines in cognition over time. Slower declines in grip strength were associated with slower declines in memory and reasoning. There was an indirect effect of BMI on cognition through changes in grip strength in the memory and reasoning outcomes, such that, a higher BMI was associated with accelerated declines in grip strength, which in turn were associated with accelerated declines in cognition. These findings are provocative given the large body of research in older adults suggesting that excess weight is protective against cognitive declines.

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Chapter 1. Introduction

The US is currently in the midst of a profound demographic shift as the population rapidly ages. Within 20 years, older adults will comprise almost one-quarter of the population (US Census Bureau, 2011). Unlike their predecessors, this group of older adults will be better educated, more racially diverse, and less impoverished compared to previous generations. Despite these advantages, individual's quality of life may be significantly diminished by deteriorating cognitive abilities as a result of chronic conditions, poor diets, and sedentary lifestyles. In fact, evidence suggests recent cohorts of older adults are experiencing more disability compared to previous cohorts (Lin, Beck, Finch, Hummer, & Master, 2012; Palacios-Ceña et al., 2012). Furthermore, these increases coincide with rapidly increasing rates of cognitive impairments. It has been estimated that by the year 2050 the incidence of dementia will increase by 100% (Brookmeyer & Gray, 2000). This has huge public health implications given the astronomical healthcare costs associated with the disorder; in 2010 the cost of dementia in the US ranged from \$157 billion to \$215 billion (Hurd, Martorell, Delavande, Mullen, & Langa, 2013).

Rates of chronic conditions associated with disability and cognitive impairment are increasing. In 2009-2010, 38% of adults aged 65 and older were obese, compared with only 22% in 1988-1994 (Federal Interagency Forum on Aging-Related Statistics, 2012). Research has shown obesity is related to diabetes mellitus (DM) (Barnes, Alexopoulous, Lopez, Williamson, & Yaffe, 2006; Kivipelto et al., 2001a, 2001b; Notkola et al., 1998; Whitmer, 2007), which is a risk factor for all-cause dementia (Cheng, Huang, Deng, & Wang, 2012). Concurrently, rates of DM have increased; in

1997-1998, 13% of adults over the age of 65 were diagnosed with DM and that number had almost doubled to 21% in 2009-2010 (Federal Interagency Forum on Aging-Related Statistics, 2012). Overweight body mass index (BMI) has been associated with a 35% increased risk of Alzheimer's disease (Anstey, Cherbuin, Budge, & Young, 2011). The proportion of any dementia attributable to obesity was 12%, whereas 21% of Alzheimer's disease (AD) risk was attributable to obesity (Beydoun, Beydoun, & Wang, 2008).

In spite of a strong association with age, some types of dementia are still considered preventable through a number of potentially modifiable risk factors (e.g., cognitive and physical activity, DM, obesity, and hypertension). Moreover, cognitive impairments associated with chronic conditions account for approximately 24% of cognitive impairment without dementia (Plassman et al., 2008). Research in this area of modifiable risk factors is very exciting given that delaying the onset of AD by five years could cut its incidence in half (Pasinetti, Wang, Porter, & Ho, 2011). Almost three million cases of AD in the US are attributable to modifiable risk factors and are known to increase risk of disability (Alley & Chang, 2007; Beavers, Miller, Rejeski, Nicklas, & Krichesvsky, 2013; Fried & Guralnik, 1997). Reducing these factors by 10-25% could prevent almost 500,000 cases of AD in the US alone (Table 1; Barnes & Yaffe, 2011). This could result in substantial benefits through improved quality of life, prolonged independence, and reduced cost to the health care system (Larson et al., 2006).

Some have argued that up to 33% of life expectancy gains attributable to public health interventions are negated by the increasing prevalence of obesity (Neovius, Rasmussen, Sunstrom, & Neovius, 2010; Stewart, Cutler, & Rosen, 2009). The World Health Organization predicts that overweight and obesity may soon overtake traditional

public health concerns, like under-nutrition, as the most significant cause of poor health (Loscalzo et al., 2008). Given the current obesity crisis, it is imperative to understand how obesity is related to negative health outcomes including functional and cognitive impairments in older adults.

Table 1. Alzheimer’s disease cases attributable to modifiable risk factors

| | Population prevalence | PAR (confidence range) | Number of cases attributable (confidence range) |
|----------------------|-----------------------|------------------------|---|
| Diabetes | 8.7% | 3.3% (1.5-5.4) | 1,740 (770-2,880) |
| Midlife hypertension | 14.3% | 8.0% (2.2-15.1) | 4,250 (1,190-7,980) |
| Midlife obesity | 13.1% | 7.3% (4.3-10.8) | 3,860 (2,260-5,700) |
| Physical inactivity | 32.5% | 21.0% (5.8-36.6) | 11,150 (3,080-19,420) |
| Low education | 13.3% | 7.3% (4.4-10.3) | 3,860 (2,360-5,440) |

Table adapted from Barnes & Yaffe, 2011; PAR: Population Attributable Risk

Although most research has focused on functional declines that occur after cognitive impairment, in light of current obesity trends, it is important to explore how obesity-related functional limitations increase the risk of cognitive impairments. Dramatic increases in chronic conditions independently associated with cognition suggest that the risks faced by today’s older adults may be substantially different from those of previous generations. It is therefore, worthwhile to explore how obesity and physical performance are associated with cognition in older adults.

Cognitive Health

Cognitive health in older adults is not merely the absence of disease, but rather the preservation of multi-dimensional cognitive abilities that allow older adults to maintain independent living and social relationships, recover from illness, and cope with normal functional declines associated with aging (Hendrie et al., 2005). Because

cognitive health is a relatively new concept with no agreed upon definition, important caveats must be mentioned. Unlike physical health parameters (e.g., blood pressure) in which there exist gold standards of measurement (e.g., sphygmomanometer) and absolute standards across individuals (e.g., 120/80mmHg is considered normal blood pressure across individuals), the parameters of cognitive health are less easily defined. Large interindividual differences in baseline levels of cognitive ability make it difficult to define what is normal. Moreover, longitudinal studies consistently report that while mean scores on cognitive tests decline over time, the standard deviation around the mean increases (Christensen, 2001; Hendrie, Purnell, Wicklund, & Weintraub, 2010) which may be exacerbated by health conditions (Salthouse, 2000).

To define ‘normal’ cognitive aging one must take into account interindividual differences in trajectories of cognitive decline along with interindividual differences in premorbid abilities (Hendrie et al., 2010). For example, for a 75-year-old with a premorbid ability in the 90th percentile, test scores in the average range (e.g., 50th percentile) represent a significant decline; whereas a 75-year-old with a premorbid ability in the 40th percentile, test scores in the average range may represent stable cognitive functioning. Twin studies suggest genetics may explain a significant portion of variability in individuals’ cognitive performance with heritability estimates (i.e., the proportion of observable differences between people that is due to genetic influences) ranging from 68% for monozygotic twins to 56% for dizygotic twins (Carmelli, Swan, DeCarli, & Reed, 2002; Swan & Carmelli, 2002; Swan et al., 1999).

Table 2. Factors influencing later life cognitive health

| Physical | Cognitive | Emotional | Behavioral |
|------------------------|-------------------|------------------|----------------------------|
| Cardiovascular disease | Cognitive reserve | Anxiety | Alcohol use |
| Diabetes | Education | Depression | Cognitive engagement |
| Hyperlipidemia | AD | Self-efficacy | Diet/nutrition |
| Hypertension | MCI | Self-esteem | Exercise/physical activity |
| Frailty | Vascular dementia | Stress | Social engagement |
| Obesity | | | Substance Use |
| Osteoporosis | | | Tobacco Use |
| Sarcopenia | | | |
| Stroke | | | |

Adapted from Rebok, Parisi, & Kueider, 2014

To further complicate the issue, multiple factors influence cognition (Table 2).

Higher educational attainment and socioeconomic status, greater physical activity, and a healthy diet positively affect cognitive functioning (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Blankevoort et al., 2010; Colcombe & Kramer, 2003; Kramer et al., 2006). Conversely, diabetes, hypertension, obesity, and negative affective states (e.g., depression and anxiety) are all negatively associated with cognitive functioning (Bourdel-Marchason et al., 2010; Hughes & Ganguli, 2009; Kivipelto et al., 2001a, 2001b, 2005; Notkola et al., 1998; Solomon et al., 2009; Spira et al., 2011; Sullivan et al., 2008; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005).

Cognition in later life

Cognition encompasses multiple processes including attention, executive function, language, memory, processing speed, and visuospatial abilities. Even in the absence of pathology, aging is associated with changes in cognition as well as structural and functional changes in the brain (Driscoll et al., 2009; Rebok & Folstein, 1993).

Cognitive performance, even in healthy older adults, may diminish as a result of cognitive resources shifting to accommodate changes in hearing, vision, and processing

speed (Salthouse, 2000) associated with normal aging. However, normal aging does not affect specific cognitive abilities to the same degree. By age 40 processing speed declines by approximately 20%; it declines by 40-60% by age 80 (Christensen, 2001). Semantic memory, or crystallized intelligence, is not as affected by normal age-related declines and may even improve with accumulated experience. In fact, older adults may depend on their accumulated knowledge to compensate for deficits in other cognitive domains. On the other hand, episodic memory (i.e., for recent events or stimuli) is the most affected by normal aging, and it is common for many older adults to report problems with their memory (Palmer & Dawes, 2010). Craik (2008) also noted that older adults often have difficulty with tasks that require the retrieval of specific information (e.g., word list recall) as opposed to general knowledge (e.g., vocabulary).

Cognitive impairments

Whereas some individuals remain relatively cognitively healthy well into old age, others develop more severe cognitive impairments, including dementia. The most common forms of dementia are Alzheimer's disease (AD), which accounts for almost 70% of all dementias, and vascular dementia (VaD), which accounts for about 15% all of all dementias (Duron & Hanon, 2008). Dementia prevalence is around 6.4% while the incidence rate in North America is 10.5 per 1,000 (Ferri et al., 2005) and ranges from 18.2 to 30.4 per 1,000 in middle-income countries (Prince et al., 2012). The incidence of AD doubles with every 5-year increase in age and between the ages of 90-95 may be as high as 30-40% (Kukull & Ganguli, 2000).

Mild cognitive impairment (MCI) is a symptomatic non-dementia phase of cognitive decline that can be a prodrome for the development of dementia (Albert, 2011).

MCI is often associated with mild problems in memory and other cognitive abilities that do not interfere with everyday functioning. Individuals with these problems are less efficient, require more time to complete tasks, and make more errors when performing these tasks compared to the past (Albert et al., 2011). Typically persons with MCI score 1.0 to 1.5 standard deviations below the mean for their age- and education-matched peers on neuropsychological tests (Albert et al., 2011). Persons with MCI who have deficits in memory and other cognitive domains are a particularly high risk group for developing AD. In fact, episodic memory impairments are highly predictive of which individuals with MCI convert to AD (Albert et al., 2011); approximately 10-15% of persons with MCI will convert to AD annually (Tabert et al., 2006). The high conversion rates taken together with the overlapping neuropathological and genetic features of MCI, suggest a strong link between MCI and AD (Kensinger, 2009).

Briefly, AD is a pathological form of aging in the brain marked by the build-up of extracellular amyloid plaques and development of intracellular neurofibrillary tangles, which appear first in the entorhinal cortex of the limbic system, followed by the hippocampus, the temporal and parietal cortices, and finally the frontal lobes (Braak & Braak, 1991). Understanding the pathogenesis of AD has been a major focus of research, and significant progress has been made in the last 20 years. One of the most consistent findings is the deposition of amyloid- β ($A\beta$), resulting in neuritic plaques that are a hallmark of the disease. This has led many researchers to hypothesize that the accumulation of $A\beta$ in the brain is the key abnormality driving AD. Amyloid precursor proteins (APP), which result in the production of $A\beta$, also play an important role. APP is present in a variety of locations throughout the body including the heart, spleen, and

liver, as well as neurons and fibroblasts (Selkoe et al., 1988). Previous research has linked A β levels directly with BMI in young, non-demented individuals (Balakrishnan et al., 2005).

Cognitive deficits associated with AD parallel structural declines and may begin with memory impairments. Deficits in episodic memory are considered a core sign in early-onset AD because the earliest pathological changes in the disease process destroy neurons in the hippocampus and entorhinal cortex. Mild-to-moderately impaired individuals with AD have deficits in executive function, language, and visuospatial abilities (Albert, 2011; Brandt et al., 2009).

Increasing age (Hughes & Ganguli, 2009), race (Tang et al., 2001), lower educational attainment (Albert et al., 1995; Bennett et al., 2003; Schaie, 2005), lower socioeconomic status (Hughes & Ganguli, 2009), depression (Bebbington et al., 2003; Spira et al., 2011), and ApoE ϵ 4 (Ballard et al., 2011; Cosentino et al., 2008; Duron & Hanon, 2008; Kozauer et al., 2008; Notkola et al., 1998) are associated with an increased risk of cognitive impairment and AD. Cognitive reserve, the ability to handle age- and pathologically-related changes in the brain without developing clinical signs or symptoms of disease (Fratiglioni & Wang, 2007), helps to explain the relationship between educational attainment and risk of dementia. Epidemiological studies have reported a higher prevalence of dementia (Gurland et al., 1999) and higher incidence of AD (Tang et al., 2001) in older African Americans compared to older Whites. Even in the absence of ApoE ϵ 4, African Americans are 4-times more likely to develop the disease than their White counterparts (Tang et al., 2001). Research suggests that ethnic differences in rates of dementia are not attributed to differences in age, sex, or education, but rather seem to

be driven by differences in cardiovascular factors and cognitive reserve (Ng, Leong, Chiam, & Kua, 2010).

Physical Health

Epidemiological studies have found both vascular and metabolic conditions increase the risk of cognitive decline and AD, with the presence of more risk factors associated with greater risk (Kivipelto et al., 2005). In addition, vascular disease has been suggested as a possible mechanism by which depression increases the risk of cognitive decline (Kohler, van Boxtel, Jolles, & Verhey, 2011). Chronic conditions have been causally related to neuronal loss, and are thought to contribute to cognitive decline (Whitmer et al., 2005). In fact, results from the ACTIVE study revealed that hypertension was associated with faster declines on logical reasoning tasks, while diabetes was associated with accelerated declines on processing speed (Kuo et al., 2005). However, in cross-sectional studies, medical conditions only explain a small fraction of variance in cognitive test scores (Verhaeghen, Borchelt, & Smith, 2003; Zelinski & Gilewski, 2003). Compared to Whites, African Americans generally have a higher incidence and prevalence of chronic health conditions (e.g., diabetes, hypertension, stroke, and vascular disease) placing them at a disproportionately greater risk for cognitive, functional, and physical impairments (Carson et al., 2011; Clark, Mungai, Stump, & Wolinsky, 1997; Evans et al., 2003; Tang et al., 2001; Whitfield, Allaire, & Wiggins, 2004).

Obesity

Obesity is a serious health problem resulting from excess body fat which significantly increases the risk of multiple negative health outcomes. Heritability

estimates for body mass index (BMI) range from 16-85% (Yang, Kelly, & He, 2007), indicating that although genetic influences are important to consider when studying obesity, they are not sufficient to explain the current obesity epidemic. Negative health consequences of obesity fall into two categories: effects attributable to the increased adipose tissue (e.g., Type 2 DM, cardiovascular disease, and hyperlipidemia), the largest endocrine gland in the body, and those attributable to increased weight, like arthritis and osteoarthritis (Bourdel-Marchason et al., 2010; Kivipelto et al., 2001a, 2001b, 2005; Notkola et al., 1998; Solomon et al., 2009; Sullivan et al., 2008; Whitmer et al., 2005).

On average, body weight tends to decrease after age 60, while at the same time fat is redistributed toward more abdominal regions. Obesity is generally defined using BMI which is a measure of weight adjusted by height and is thought to capture overall adiposity. However, BMI does not adequately define obesity across the life span. The loss of lean body mass and height that occurs with aging can make BMI cut points inappropriate in older adults because the loss of height results in an overestimation of fat, whereas a decrease in lean body mass underestimates fat (Waters & Baumgartner, 2011). Accuracy of BMI depends on whether subjective or objective measurements are taken. Many adults are unsure of their actual weight and height and have a tendency to overestimate height (Haboubi, Hudson, & Pathy, 1990; Vailas & Nitzke, 1998). Unreliability of self-reported height and weight increases with age (Kuczmarski, Kuczmarski, & Najjar, 2001).

BMI is also affected by sex and ethnicity (Ho et al., 2010; Jeong et al., 2005). Women tend to be overrepresented in the highest BMI categories (Flegal et al., 1998; Larrieu et al., 2004), and there is some evidence of a sex difference in the association

between adiposity and cognitive function. For example, findings from the Framingham study (Elias et al., 2005) showed that obese men, but not women, performed significantly worse on some cognitive tasks. However, other studies report no sex differences in the association between weight and cognitive function (Hassing et al., 2010).

Two sex hormones, testosterone and estrogen, may explain differences. In men, there is a bidirectional relationship between adiposity and testosterone levels such that low levels of testosterone and central obesity are both predictors and consequences of each other (Pelusi & Pasquali, 2012). Not only are low testosterone levels linked with obesity risk, they have also been implicated in reduced cognitive functioning in older men (Beauchet, 2006). In both men and women, the production of estrogen by adipose tissue constitutes a significant proportion of total estrogen production. Estrogen regulates synaptic connectivity and neuronal structure in the brain (Kramarova, Wright, & Pongratz, 2009).

Obesity is rapidly increasing in the US; in those aged 60 and older around 72% are overweight or obese, while over 35% are obese (Beydoun, Beydoun, & Wang, 2008). This is a relatively new trend in the US; from 1960 to 1980 the prevalence of overweight and obesity among adults was relatively constant and only began to increase around the mid-1980s (Flegal, 2005). These increases were seen across all demographic groups regardless of smoking status (Pasinetti et al., 2011). As with AD, obesity has placed a huge burden on the health care system, with an estimated 10% of all medical spending US adults attributable to obesity. Individually, obese adults spend 36% more annually on medical expenses compared with normal weight adults (Finkelstein, Fiebelkorn, & Wang, 2003).

Obesity and cognition

Studies of obesity and cognition in children and adolescents provide substantial evidence that obesity is associated with impaired cognitive functioning, independent of cardiovascular and socioeconomic risk factors (Smith et al., 2011). Poorer cognitive functioning in childhood has been linked with obesity and Type 2 diabetes in adults (Osika & Montgomery, 2008). Nine cross-sectional studies examined the effects of obesity in children aged 4-18 years with fairly consistent findings showing poorer cognitive functioning in obese children compared with their normal weight counterparts. Deficits were noted in areas of memory, attention, executive function, global functioning, and verbal abilities (Smith et al., 2011). Executive function, a higher order cognitive ability which facilitates initiation, planning, regulation, and achievement of goal-directed behaviors, is one of the most consistent cognitive deficits reported in obese children and adolescents (Cserjesi, Molan, Luminet, & Lenard, 2007; Li, Dai, Jackson, & Zhang, 2008; Lokken, Boeka, Austin, Gunstad, & Harmon, 2009; Mond, Stich, Hay, Kraemer, & Baune, 2007; Reinert, Po'e, & Barkin, 2013; Verdejo-García et al., 2010).

A study by Li et al. (2008) which included over 2,000 children found overweight BMI (≥ 95 th percentile) was independently associated with worse performance on tests global functioning, working memory, and attention even after adjustment for socioeconomic status and other potential confounders. To further support these findings, a longitudinal cohort of 7,990 children followed from age 7 to 33 revealed that poor performance on measures of executive and motor abilities at age seven predicted obesity at age 33, even after adjusting for sex, social class, general motor disability, mental retardation, social adjustment score, and BMI at age 7; indicating that childhood BMI

was not responsible for the observed differences in executive and motor abilities (Osika & Montgomery, 2008). These findings could suggest a predisposition to obesity which includes dysregulation in neural circuits associated with the orbital-frontal cortex, an area of the brain associated with inhibitory control, a component of executive function (Willeumier, Taylor, & Amen, 2011). The negative association between obesity and executive function in adolescents may be driven by the disposition of body fat, such that fat stored viscerally is more detrimental than fat stored elsewhere (Schwartz et al., 2013).

Obesity is associated with structural and functional changes in the brain. Brain imaging studies have revealed that obesity is associated with lower brain volumes in older adults who are cognitively normal (Raji et al., 2010) as well as those with MCI and AD (Ho et al., 2010). Obese older adults show atrophy in the frontal lobes, anterior cingulate cortex, hippocampus, and thalamus (Raji et al., 2010). Furthermore, obese individuals have significantly lower gray matter in areas of the brain associated with taste, reward, and behavioral control (Pannacciulli et al., 2006).

Research suggests there is a possible link between obesity and dopamine, brain-derived neurotrophic factor (BDNF), and brain morphology. Obesity and cognition have been associated with dopaminergic genes (Ariza et al., 2012) and dopamine pathway dysregulation (Ariza et al., 2012; Skoranski et al., 2013; Volkow, Wang, & Baler, 2011; Wang, & Baler, 2011). Imaging findings corroborated this; reductions in dopamine receptors have been associated with decreased metabolism in the prefrontal regions in obese adults, where an inverse relationship between dopamine receptors and BMI has been described (Volkow et al., 2008; Wang et al., 2001). In otherwise healthy individuals, those with the highest BMI had lower prefrontal metabolic activity (Volkow

et al., 2008; Willeumier, Taylor, & Amen, 2011). BDNF, found in high concentrations in the cerebral cortex and hippocampus, is important for long-term memory (Bekinschtein et al., 2008) and has recently been link to regulation of body weight (Rios, 2013). These mechanisms may account for the association between obesity and cognitive performance. Older adults with higher systolic or diastolic blood pressure in the presence of a high BMI or greater waist circumferences showed an impaired ability to initiate motor responses (Waldstein & Katzel, 2006). The supplementary motor areas in the brain are affected by hypertension (Gąsecki et al., 2013) which may explain why obese older adults are slower to initiate motor responses.

Several mechanisms have been proposed to explain how obesity may influence cognitive functioning. These mechanisms include elevated triglycerides and blood pressure, impaired insulin regulation, and systemic inflammation. Obesity can impact cognition through direct and indirect pathways. Direct pathways involve adipose tissue and its effects on the brain which will be discussed in greater detail in Chapter 2. Indirect pathways can result from poor dietary choices that lead to weight gain and/or increased risk of multiple disorders associated with obesity which have all been independently associated with decreased cognition functioning. In older adults research has shown that overweight and obesity are related to self-reported functional limitations (Jensen & Friedman, 2002), performance-based functional disability (Davis et al., 1998), DM, hypertension, and hyperlipidemia (Bourdel-Marchasson et al., 2010; Cheng et al., 2012; Sullivan et al., 2008).

Moreover, BMI is a strong predictor of muscle mass. Using data from NHANES III a variety of comorbid conditions, including diabetes and coronary heart disease, serve

as independent predictors of lower muscle strength and also modified the relationship between muscle mass and obesity. For instance, older adults with diabetes had poorer muscle quality relative to non-diabetics suggesting that greater muscle mass does not always indicate greater muscle strength (Chen, Nelson, Zhao, Cui, & Johnston, 2013). Sarcopenia is a degenerative loss of muscle mass and strength associated with aging (Cruz-Jentoft et al., 2010) and impaired cognitive functioning (Nourhashémi et al., 2002). Functional complications of sarcopenia include the loss of muscle strength which can lead to disabilities in mobility and IADLs and increases the risk of falls (Baumgartner et al., 2004). Results from the Health ABC Study reported older adults aged 70-79 with low muscle strength were more likely to develop mobility limitations (Visser et al., 2005). Sarcopenic obesity, a combination of low lean body mass and high fat mass, is rapidly increasing in older adults (Baumgartner et al., 2004; Bouchard, Dionne, & Brouchu, 2009) and affects 9-15% of men and 7-22% of women (Zamboni et al., 2005; Zoico et al., 2004).

Dementia has a long prodromal phase in which appetite is severely decreased leading to significant weight loss and under nutrition. A meta-analysis (Anstey et al., 2011) found older adults who were underweight or obese had the highest risk of developing AD in later life compared to those with normal weight (Risk Ratio ~ 2.0). Overweight BMI was associated with a 35% increased risk of AD, 33% increased risk of VaD, and a 26% increased risk of any dementia. Some research suggests slightly overweight older adults are protected against cognitive decline (Atti et al., 2008). The inclusion of individuals in a preclinical phase of dementia muddies the relationship between BMI and cognition because it has been established that individuals often lose

weight in the early stages of disease (Stewart et al., 2005; White, Pieper, & Schmader, 1998).

Results from longitudinal studies suggest obesity and underweight in midlife are also associated with lower cognitive function. A cohort study with over 20 years of follow-up reported individuals with long-term obesity or long-term underweight had lower cognitive functioning in late midlife (Sabia et al., 2009). Similar results were noted in the population-based Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study. Although the association was somewhat attenuated after adjusting for sociodemographic variables and midlife vascular risk factors (i.e., blood pressure, total cholesterol level, smoking status, ApoE genotype, and history of vascular disorder), the association still remained significant. Midlife obesity, high total cholesterol levels, and high systolic blood pressures were all found to be significant risk factors for dementia with odds ratios around two for each factor. A combination of these midlife risk factors increased the risk of dementia and AD additively; an individual with all three factors had an odds of AD 6.2 times higher than those without those factors (Kivipelto et al., 2005). Furthermore, a prospective study using the Swedish Twin Registry reported that midlife BMI predicted cognitive functioning 30 years later in a dementia-free sample. Even after controlling for lifestyles factors (i.e., smoking and alcohol use), midlife physical activity and vascular disorders, midlife BMI was a significant predictor of all cognitive domains measured (i.e., short- and long-term memory, speed, verbal and spatial ability); however, with the exception of verbal abilities, higher midlife BMI was not associated with faster rates of cognitive decline (Hassing et al., 2010). Additional analyses indicated that twin individuals aged 65 and older who were overweight (OR = 1.71; 95% CI: 1.30-2.25) or

obese (OR = 3.88; 95% CI: 2.12-7.11) in midlife had an increased risk of dementia, independent of diabetes and other vascular risk factors indicating early-life environmental factors and genetics play a role in the midlife obesity-dementia association (Xu et al., 2011).

Disability

The concepts of *impairment*, *functional limitation*, and *disability* are based on the work of Nagi (1965) and Verbrugge and Jette (1994) in which the disablement process was defined as an avoidable trajectory from injury to disablement. *Impairment* can be defined as deviation from what is considered normal function. A *functional limitation* is the loss of the ability to carry out an activity. In the broadest sense, *disability* can be thought of as the difference between an individual's abilities and environmental demands or the inability to perform a social role. Disability is an indicator of health status, a major determinant of quality of life, and an indirect indicator of morbidity in older adults (Sauvaget, Tsuji, Aonuma, & Hisamichi, 1999).

The onset of disability can be ascribed to two distinct processes; one the result of underlying chronic diseases associated with aging, and the other results from acute events such as stroke or hip fracture. The most commonly used measures of disability are self-reports of basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs). In the disablement process, these domains are affected in a hierarchical manner such that mobility loss occurs first and is then followed by mobility issues plus difficulties with IADLs, and finally, the accumulation of difficulties in mobility, IADLs, and ADLs (Barberger-Gateau et al., 2000).

Differential risk by sex and race

Cognitive functioning, age, sex, race, and education can modify the impact of disease on disability (Fried & Guralnik, 1997). Consistently, the prevalence of disability is higher in women aged 65 years and older than in men (Fried & Guralnik, 1997; Friedman, Elasy, & Jensen, 2001; Wray & Blaum, 2001); however this sex difference may disappear in the oldest-old (Berlau et al., 2012). Higher disability prevalence in women, coupled with women's longer life expectancies, means older women, on average, spend more years living in a disabled state (Dunlop, Hughes, & Manheim, 1997). Furthermore, it appears that the onset of disability occurs earlier in women (Dunlop et al., 1997).

These sex differences could have several possible explanations. First, a higher prevalence of fatal conditions in men and non-fatal conditions in women may explain sex differences (Gold et al., 2002). Hammond's (1995) theory of "multiple jeopardy" has been used to describe how women with a combination of disadvantages, including lower income, less education, and widowhood, have a higher risk for negative health outcomes compared to older men. Second, socio-cultural roles may be driving these differences. Several researchers have suggested that IADL items related to household activities should be excluded for men because these activities are usually performed only by women (Avlund, 1997; Lawton & Brody, 1969). Dropping these IADL items would lead to a more homogenous measure that is less influenced by sex-roles and is more sensitive to actual functional limitations.

With aging comes increased heterogeneity. Cumulative advantage and/or disadvantage theory can be used to explain findings on the increased heterogeneity seen

in later life. Cumulative advantage can be traced to the late 1960s when Merton (1968) coined the phrase “the Matthew effect.” The theory has been broadly applied to multiple domains of research but in general states that early advantaged leads to accelerating advantage over time. Early advantages could include many factors such as access to education, higher socioeconomic status, or identifying as part of the racial majority. Older adults can experience a cascade of health and social disadvantages over the course of their life. An individual’s cognitive and physical health trajectories are then influenced by the accumulation of these events.

African Americans have a greater risk of disability compared to Whites (Clark, 1997; Clark & Maddox, 1992; Clark et al., 1997; Kelley-Moore & Ferraro, 2004; Mendes de Leon et al., 2005). Although African Americans have a greater risk of disability, Whites are more likely to suffer from compromised bone strength predisposing them to an increased risk of fracture (Cauley, 2011; Hochberg, 2007). These findings would suggest that the increased risk of disability in African Americans is not due to compromised bone strength but rather chronic diseases and/or genetic predispositions. There is still debate as to whether racial disparities disproportionately affect African American women. A number of studies have shown that racial disparities in risk factors for disability tend to be greater in African American women compared to African American men. For instance, African American women have a higher prevalence of cardiovascular disease, diabetes, and obesity compared to White women, and these differences are larger than those observed between African American and White men (Carson et al., 2011; CDC, 2005; Clark et al., 1997; Friedman et al., 2001; Gold et al.,

2002; Kelley-Moore & Ferraro, 2004; Mendes de Leon et al., 2005; Whitfield, Altaire, & Wiggins, 2004).

Mobility disability

Mobility disability is the most common form of disability in community samples, has dramatic effects on activities in everyday life (Ebrahim, Wannamethee, Whincup, Walker, & Shaper, 2000), and is associated with physical, sensory, and cognitive deficits (Anstey, Wood, Lord, & Walker, 2005). Mobility encompasses a broad spectrum that ranges from simple tasks like the ability to move one's body, to more complex tasks that involve life- and driving-space (Wood et al., 2005). Mobility impairments refer to the lack of muscle strength required to ambulate, lift heavy objects, or grasp items. Lower body mobility impairments may require the use of an assistive device, such as a cane, wheelchair, or walker. Multiple tests have been proposed as a measure of mobility impairments, large-scale epidemiological studies have included both subjective measures, like the SF-36, ADLs, and IADLs, as well as objective measures like chair-stands, muscle strength (e.g., handgrip strength, arm and leg abduction, flexion, and extension), and gait speed (Buchman, Wilson, Boyle, Bienias, & Bennett, 2007; Choquette et al., 2010; Clouston et al., 2013; Mijnaerends et al., 2013).

Grip strength, which will be used in the current proposal as a measure of physical functioning, has long been thought of as a proxy for overall body strength (Choquette et al., 2010; Rantanen et al., 1999; Sallinen et al., 2010; Shinkai et al., 2000). Attractive features of the handgrip strength measure, including ease of administration and low cost, make it more feasible in large-scale epidemiological studies compared to other measures

like the Short Physical Performance Battery (Guralnik et al., 1994), which take longer to administer and score.

Grip strength is also implicated in the disablement process. Handgrip strength has been used in multiple studies to predict future ADL disability in community-dwelling older adults. Men and women in the lowest quartiles of handgrip strength have a higher risk of overall disability (Giampaoli et al., 1999; Gill, Murphy, Barry, & Allore, 2009) as well as ADL disabilities compared to those with better handgrip strength (Al Snih, Markides, Ottenbacher, & Raji, 2004; Ishizaki, Watanabe, Suzuki, Shibata, & Haga, 2000; Shinkai et al., 2003). Furthermore, handgrip strength has been associated with an increased risk of AD. Buchman and colleagues (2007) examined handgrip strength in relation to cognitive and physical performance. They found that for each 1-lb annual decline in grip strength the risk of AD increased 9%. Participants were screened for AD at baseline and those who developed the disease during the first five years of follow-up were excluded from all analyses. These results suggest that not only does higher grip strength at baseline protect against AD, but more importantly, physical declines may in fact, precede the onset of cognitive declines. It is possible that both grip strength and cognitive decline share similar etiopathogenesis, like impaired neural circuits.

The SF-36, a measure of health-related quality of life, has been used to measure disability in older adults (Syddall et al., 2009). Specifically, the Physical Functioning (PF) subscale has been validated as a measure of mobility disability in epidemiologic studies of older adults (Syddall et al., 2009). In the ACTIVE study hypertension and diabetes, both independently associated with obesity and an increased risk of disability, were associated with faster rates of decline on the SF-36 PF subscale (Kuo et al., 2005).

To our knowledge, the association between BMI, grip strength, and cognitive performance has not been examined in longitudinal cohorts of older adults.

Obesity may be strongly linked with mobility limitations and disability because added weight makes it more difficult to ambulate. In fact, results from the Health, Aging and Body Composition study suggest higher BMI was associated with increased risk of mobility limitations (Lee et al., 2005). The Longitudinal Study of Aging (LSOA), a prospective survey of 5,000 community-dwelling older adults aged 70 years and older, explored patterns of change and a hierarchy of disability in ADLs. The progression of incident disability began with difficulties in walking and was followed by difficulties in bathing, transferring, dressing, toileting, and feeding (Dunlop et al., 1997).

Disability and weight

The increasing prevalence of obesity in older adults has a profound impact on mobility disability. During 1988-2004 the likelihood of functional impairment increased over 40% in obese older adults (Alley & Chang, 2007). Consequently, disability rates are predicted to dramatically increase (Sturm, Ringel, & Andreyeva, 2004). Data from NHANES III highlight this trend; among obese individuals 37% reported disability in 1994, whereas in 2004, 42% reported disability and functional impairments (Alley & Chang, 2007). A meta-analysis of obesity and mobility disability in older adults reported consistent findings linking high BMI (especially those $\geq 35 \text{ kg/m}^2$) with an increased risk of mobility disability (Vincent, Vincent, & Lamb, 2010). These results were extended to the disability domains of IADLs and ADLs, in which obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) older adults aged 65 and older had the highest risk of disability compared with normal weight older adults (Larrieu et al., 2004). Similar to the relationship between BMI and dementia,

the relationship between BMI and physical disability is curvilinear. There is a beneficial effect associated with older adults being slightly overweight (i.e., BMI 25-29.9 kg/m²; Rejeski, March, Chmelo, & Rekeski, 2010); however, once older adults cross the Class II obesity threshold (BMI \geq 35 kg/m²), the risk of physical disability increases significantly (Al Snih et al., 2007; Ferraro, Su, Gretebeck, Black, & Badlay, 2002; Mendes de Leon, Hansberry, Bienias, Morris, & Evans, 2006; Rejeski et al., 2010).

There are multiple pathways in which obesity can increase the risk of disability in older adults. Direct effects are attributable to the increased risk of musculoskeletal conditions, like arthritis, which make it more difficult to successfully navigate the environment. Among a nationally representative sample, the odds of arthritis and osteoarthritis were seven times higher for obese individuals compared to their normal weight peers. Furthermore, of those with arthritis or osteoarthritis, obese individuals reported more pain and stiffness, poorer function, greater disease severity, and lower health-related quality of life (Ackerman & Osborne, 2012). The increased risk of diabetes and cardiovascular disease caused by obesity can indirectly influence disability risk. Although it was previously noted that BMI may not be the best indicator of adiposity in older adults, a recent study of multiple adiposity measures (i.e., BMI, waist and hip circumference, fat mass, fat-free fat mass, and percentage fat) found that for both men and women, BMI was the single best predictor for multiple types of disability (Wong et al., 2012).

Weight loss in older adults remains controversial and is due to concerns regarding loss of lean muscle mass and physical function (Miller & Wolfe, 2008). Data from three randomized controlled trials of intentional weight loss in older adults were combined to

examine the association between changes in fat and lean mass and changes in physical function in overweight and obese individuals (Beavers et al., 2013). Intentional weight loss was associated with significant improvements in self-reported mobility disability. Importantly, fat mass loss was a stronger predictor of changes in physical function compared to lean mass loss (Beavers et al., 2013). However, others suggest that weight loss is not protective against the development of mobility limitations in overweight and extremely obese older adults (Lee et al., 2005). Although weight loss is important when discussing the link between weight and cognition, the ACTIVE study was not able to differentiate between intentional and unintentional weight loss. Intentionality of weight loss is an important factor which can help to determine if weight loss is the result of disease/unrecognized health problems or due to changes in diet and/or exercise (Lee et al., 2005). Because the ACTIVE study is unable to determine intentionality of weight change, weight loss was not explored in the current proposal.

With normal aging comes a progressive loss of muscle mass and an increase in fat mass (Schultz, Kyle, & Pichard, 2002). Accumulation of fat within muscle leads to lower quality muscle that is less capable of generating strength and power for mobility-related tasks (Marks, 2007) significantly increasing the risk of disability in older adults. A meta-analysis of over 135,000 middle-aged and older adults (Backholer, Wong, Freak-Poli, & Peeters, 2011) revealed a stepwise increased risk of ADL limitations in overweight (OR=1.04; 95% CI 1.00-1.08), Class I obese (1.16, 95% CI 1.11-1.21), and Class II (or higher) obese (1.76; 95% CI 1.28-2.41) individuals, relative to normal weight individuals. Longitudinal analyses revealed similar findings, but the magnitude was larger for each BMI category (Backholer et al., 2011). In fact, when compared with normal weight older

adults, obese older adults were more likely to report disabilities in multiple domains including mobility, IADLs, and ADL after adjustment for sociodemographic characteristics (Larrieu et al., 2004).

Although Jack and colleagues' (2010) hypothetical model of the Alzheimer's pathological cascade suggests that physical function does not begin to decline until after declines in memory, there is evidence to suggest that IADL impairments may start earlier in the disease process. Four IADL items (i.e., ability to use the phone, use of means of transportation, responsibility for medication, and ability to handle finances) were associated with current Mini-Mental State Exam (MMSE) score and predicted 1-year dementia incidence in a sample of community-dwelling older adults (Barberger-Gateau, Dartigues, & Letenneur, 1993). These results suggest that individuals with IADL-specific impairments may have a higher risk of dementia because of psychological or physical factors associated with both impairment and dementia. Another possibility is that impairment on these four IADLs is an early sign of dementia that does not meet the diagnostic threshold. It is possible that for a high risk group of older adults, especially those who are obese and have multiple chronic conditions, functional impairments may be present long before a diagnosis (Barberger-Gateau et al., 1993).

Disability and cognition

Intact cognitive functioning is necessary to complete complex tasks (e.g., managing finances) as well as the ability to successfully navigate the environment and maintain independent living status. In fact, even simple tasks like walking require a complex network of cognitive abilities (Li, Lindenberger, Freund, & Baltes, 2001). For example, attentional skills are necessary for walking, and research suggests that

attentional impairments are independently associated with future falls, postural instability, and impairment in ADLs (Woollacott & Shumway-Cook, 2002). Several groups have proposed that with increasing age, walking requires increasing amounts of cognitive and attentional processing (Li et al., 2001; Lindenberger, Marsiske, & Baltes, 2000).

Cognitive impairments, even in the absence of a dementia diagnosis, are associated with decreased quality of life and increased disability (Tabert et al., 2002). In the oldest-old (age greater than 90) cognitive impairment doubles the risk of disability (Berlau et al., 2012), whereas studies in younger cohorts have reported smaller effects (Johnson, Lui, & Yaffe, 2007).

Gill et al. (1997) demonstrated that the orientation and memory items of the MMSE had the strongest predictive value of functional status. Cognitive data from the Second Longitudinal Study of Aging (LSOA II) were used to predict functional disability in later life. Individuals with lower scores on measures of mental status and memory were more likely to die or become disabled on IADLs and ADLs (OR=1.58; 95% CI: 1.15-2.16) compared to those with higher scores (McGuire, Ford, & Ajani, 2006). In a nationally representative study of older adults, prevalent and incident IADL and ADL limitations were independently associated with lower baseline cognitive scores but not faster rates of decline. This suggests disabilities negatively affect cognitive performance at the time of their onset but may not lead to deterioration over time (Chodosh, Miller-Martinez, Aneshensel, Wight, & Karlamangla, 2010). Executive functioning, which involves planning and execution of goal-directed behaviors, is necessary to successfully complete IADLs. Over six years, women with baseline executive function impairments

had significantly worse IADL and ADL function compared to women with no impairments. In contrast, women with impairments in global cognitive functioning (i.e., MMSE) did not have an increased risk of IADL or ADL dependence (Johnson, Lui, & Yaffe, 2007). In fact, executive function was a better predictor of IADL performance than depression or demographic characteristics in older adults (Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000). Processing speed may also play an important role in functional abilities (Birren, Woods, & Williams, 1980). Measures of processing speed predict IADLs (Owsley, Sloane, McGwin, & Ball, 2002) and mobility specific outcomes, such as limited life-space (Stalvey, Owsley, Sloane, & Ball, 1999).

Although physical limitations and disabilities may increase the risk of cognitive decline, the independent effects of weight and physical functioning on cognitive function and changes in cognition have not been quantified. The ACTIVE study is a unique data set that allows for the exploration of changes in cognition before and after the onset of disability.

Chapter 2. Mechanisms of Obesity

Traditionally, episodic memory is impaired in late-onset Alzheimer's disease (AD), whereas vascular dementia (VaD) is characterized by deficits in executive function/attention or frontal-lobe abilities (e.g., impaired function in social situations). Although there is great overlap in risk factors for AD and VaD, distinctive cognitive and behavioral profiles in both disorders suggest chronic health conditions with established negative effects on specific areas of the brain would differently affect risk of AD and/or VaD. Risk factors which negatively affect regions of the brain responsible for episodic memory retrieval and encoding, including the hippocampus, medial-temporal lobe and prefrontal cortex (PFC; Cabeza & Nyberg, 2009), are likely to have a stronger association with AD; whereas factors which negatively affect regions of the brain associated with attention and executive function, including the PFC and parietal lobes (Cabeza & Nyberg, 2000; Pa et al., 2010), are likely to have a stronger association with VaD. Obesity and its sequelae (i.e., hypertension, diabetes) are known to have negative effects on brain structure and function as well as cognition.

Although there is strong evidence to support a link between body weight and cognitive performance across the life span (see Smith, Hay, Campbell, & Trollor, 2011 for a review), there is still debate regarding the causal nature of the relationship and the influence of mediators (e.g., diabetes, hypertension). Studies have shown an association between obesity and cognitive performance in otherwise healthy children (Smith et al., 2011; Taras & Potts-Datema, 2005) and adults (Gunstad et al., 2007, 2008), suggesting that the association between body weight and cognition is not due only to the increased risk of conditions associated with obesity (i.e., diabetes). It is unlikely that overweight

and obese children have had time to develop the sequelae associated with long-term obesity such as atherosclerosis, hypertension, coronary heart disease, or metabolic syndrome suggesting that obesity alone may influence cognitive functioning.

Interestingly, there is evidence that impaired executive functioning may increase future risk of obesity. Findings in young children (aged 2-7 years) suggest that impaired inhibitory control, a component of executive function, is predictive of higher BMI at a later age (5.5-15 years; Reinert, Po'e, & Barkin, 2013). Dysregulation in neural circuits in the orbito-frontal cortex, an area associated with aspects of executive function, may predispose individuals to an increased risk of obesity (Willeumier et al., 2011). It is therefore possible that a bi-directional relationship between obesity and certain cognitive abilities exists.

There is clear evidence to support the link between obesity measured in early- or midlife and cognitive decline and/or dementia (Kivipelto et al., 2005; Sabia et al., 2009; Smith et al., 2011; Xu et al., 2011); however studies of obesity in later life have shown mixed (Buchman et al., 2007) or even protective results (Corley, Gow, Starr, & Deary, 2010; Elias, Elias, Sullivan, Wolf, & D'Agostino, 2005; Kuo et al., 2006). Discordant results may be attributable to differences in study design according to the choice of cognitive tests and different cognitive domains measured, length of follow-up period, definition of risk factors, type of dementia, and/or age of participants.

In conjunction with behavioral deficits, obesity has been associated with structural and functional changes in the brain. Obese individuals who are cognitively normal (Raji et al., 2010; Ward et al., 2005) as well as those with mild cognitive impairment and AD (Ho et al., 2010) have significantly reduced overall brain volume and

gray matter in areas of the brain associated with taste, reward, and behavioral control, including the PFC and the hippocampus (Pannacciulli et al., 2006; Raji et al., 2010; Ward et al., 2005).

Higher BMI is associated with less neuronal integrity (as measured by *N*-acetyl-aspartate) in the frontal, temporal, and parietal lobes, with the largest effects noted in the frontal regions (Gazdzinski et al., 2010; 2008). Frontal regions of the brain are most affected by aging which could suggest that obesity accelerates age-related changes in the brain. Decreased neural activity in the PFC has been observed in obese, but otherwise healthy individuals (Willeumier et al., 2011) and has been associated with performance on measures of memory and executive function (Volkow et al., 2009). Given the importance of the PFC and the hippocampus in cognition, the observed structural and functional changes may contribute to cognitive deficits observed in obese individuals.

Although a vast amount of research suggests that body mass is associated with cognitive functioning, the degree to which body mass is directly associated with cognitive and contributes to cognitive deficits across the life span is contentious and an area of active research. This review will focus on several potential inter-connected mechanisms through which obesity influences cognitive performance. These mechanisms involve elevated blood pressure and triglycerides, impaired insulin regulation, and systemic inflammation. Figure 1 highlights how these mechanisms are associated with cognitive functioning. Some argue that obesity does not directly influence cognition (Sellbom & Gunstad, 2012); instead, a number of related factors including insulin dysregulation and inflammation mediate the effects of obesity on brain changes and cognitive deficits. Supposing this is true, one would then expect that obesity would not be

associated with cognitive deficits in young children with no history of inflammation or insulin dysregulation. Research does not support this notion. In fact, obesity has been associated with cognitive deficits in children less than 10 years old (Reinert et al., 2013; Smith et al., 2011).

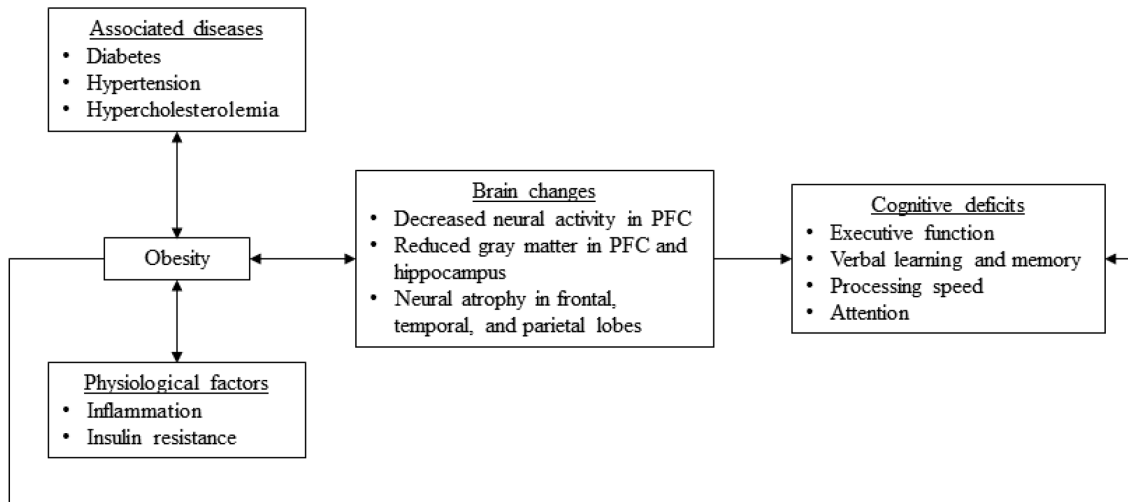


Figure 1. Obesity-related mechanisms influencing cognitive changes.

Blood Pressure

Blood pressure is considered a marker of cerebrovascular health (Gąsecki, Kwarcianny, Nyka, & Markiewicz, 2013) and even in individuals who remain normotensive throughout their life, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) increase with age. However, increased blood pressure is not an inevitable part of aging and likely results from environmental factors including lifestyle choices and social influences (Cherubini et al., 2010). The effects of blood pressure on cognition vary across the life span, where high blood pressure in middle age is associated with impaired cognition, especially in memory and reaction time (Gąsecki et al., 2013), and an

increased risk of dementia (Gąsecki et al., 2013; Kivipelto et al., 2005); whereas later in life, it is associated with a decreased risk of dementia (Ruitenberget al., 2001).

Longitudinal data show an inverted u-shaped relationship between cognitive decline and blood pressure. In the Honolulu Asia Aging Study almost 18% of dementia cases were attributable to pre-hypertensive SPB levels (120-140mmHg); whereas 27% of dementia cases were attributable to untreated midlife SPB levels ≥ 120 mmHg (Launer et al., 2010). Other findings suggest that maintaining a normal blood pressure is necessary for optimal cognitive functioning. Low SBP has been associated with impaired performance on measures of executive attention in older adults over the age of 70 (Mahoney, Verghese, Goldin, Lipton, & Holtzer, 2010) as well as poorer cognitive (i.e., MMSE) and functional (i.e., Katz IADLs) abilities in two samples of centenarians (Richmond, Law, & Kay-Lambkin, 2011; Szewieczek et al., 2011).

Age of hypertension onset also influences the risk of dementia. Several longitudinal studies with large samples find no association between hypertension and risk of AD if the diagnosis occurs after the age of 65 (Kimm et al., 2011; Posner et al., 2000); whereas a diagnosis prior to age 65 conferred a higher risk for all types of dementia (Kimm et al., 2011). These studies suggest that the negative effects of hypertension on cognition may operate with a considerable time lag. A longitudinal study of Medicare beneficiaries aged 65 and older suggests hypertension is more closely linked with vascular-related dementias and the effects on dementia risk differ according to specific comorbid vascular risk factors. History of only hypertension was associated a 2-fold increased risk of VaD, whereas a history of hypertension plus heart disease or diabetes resulted in a three-fold or six-fold increased risk of VaD, respectively (Posner et al.,

2000). In contrast, a population-based study of individuals aged 85 years or older reported that over nine years, those with a history of hypertension had a lower probability of dementia (Rastas et al., 2010).

The apparent protective effect of hypertension in very old adults may be due several factors. First, a drop in blood pressure precedes clinical manifestations of dementia in older adults, (Gąsecki et al., 2013), negatively affecting cognitive performance (Stewart, Prince, & Mann, 1999). Second, survivor bias may explain protective effects; younger individuals with poorly controlled hypertension may die sooner and therefore not live long enough to be at risk for dementia. Another possible explanation involves vascular changes associated with normal aging. A natural consequence of aging is the elongation of cerebral vessels which increases the minimal blood pressure necessary for perfusion of the white matter, increasing the risk of ischemia (Cherubini et al., 2010).

Several possible mechanisms have been explored to explain the association between midlife blood pressure and cognition later in life including high blood pressure leading to stroke (MacMahon et al., 1990), atherosclerosis (Duron & Hanon, 2008), white matter lesions (WMLs; Razay, Williams, King, Smith, & Wilcock, 2009), as well as increased hippocampal atrophy and plaques and tangles (Bourdel-Marchasson, Lapre, Laksir, & Puget, 2010). Evidence clearly shows that hypertension causes stroke (MacMahon et al., 1990) and atherosclerosis (Li & Chen, 2005), increasing the risk of vascular damage in the brain along with concurrent impairments in mobility and cognition (Hajjar et al., 2011). High blood pressure is also associated with progression of WMLs. Individuals with uncontrolled untreated hypertension had significantly more

WML progression compared with those with uncontrolled treated hypertension. Cerebral WMLs are prevalent in older adult populations and increase the risk of both dementia and stroke (Verhaaren et al., 2013).

To summarize, the link between blood pressure and cognition is a complex non-linear relationship. Both high and low levels of DBP (a marker for atherosclerosis) were related to faster declines in cognition over 5 years (Razay et al., 2009), whereas low levels of SBP were associated with impaired executive attention (Mahoney et al., 2010), global cognition and functional abilities (Richmond, Law, & Kay-Lambkin, 2011; Szewieczek et al., 2011). Chronic hypertension that begins in middle age increases the risk of cognitive decline later in life; however decreases in blood pressure are observed prior to and after the onset of dementia.

Cholesterol

Cholesterol plays a vital role in neuronal function and plasticity (van Vliet, 2012). In fact, the brain contains 25% of the total lipids in the body even though it makes up only 2% of total body weight (Dietschy & Turley, 2001). Similar to hypertension, high levels of cholesterol in midlife increase the risk of cognitive impairment and dementia; whereas in later life the association between cholesterol and cognition attenuates. A longitudinal study found that after controlling for multiple confounders (i.e., age, sex, race, education, and midlife vascular risk factors), midlife cholesterol in those aged 40-45 was associated with AD and VaD three decades later. The risk of AD increased with higher levels of cholesterol; compared to those with normal cholesterol levels (< 198mg/dl), individuals in the third quartile (221-248 mg/dl) had a hazard ratio (HR) of 1.31 (95% CI: 1.01-1.71), while individuals in the fourth quartile (249-500 mg/dl) had

the highest risk of AD (HR = 1.58, 95% CI: 1.22-2.06). Additionally, higher cholesterol is associated with worse performance on episodic memory and category fluency in later life (Solomon, Kivipelto, Wolozin, Zhou, & Whitmer, 2009). These results were replicated in the Finish cohort of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study even after controlling for ApoE genotype and other vascular risk factors (Kivipelto et al., 2002, 2005). A notable exception comes from the Prospective Population Study of Women, which followed women aged 38-60 at baseline over three decades and found no association between baseline cholesterol levels and incident AD (Miekle et al., 2010). One possible explanation for these discrepant findings is that the diagnosis of dementia was obtained using only medical records making it likely that cases of dementia were missed.

Later in life, the association between cholesterol and cognitive function/dementia becomes somewhat less clear and opposing results are common (Kuusisto et al., 1997; Li et al., 2005; Merched, Xia, Visvikis, Serot, & Siest, 2000; Mielke et al., 2005; Reitz et al., 2008; Reitz, Luchsinger, Tang, Manly, & Mayeux, 2005; Reitz, Tang, Luchsinger, & Mayeux, 2004; Romas, Tang, Berglung, & Mayeux, 1999; Tan et al., 2003; van den Kommer et al., 2009). Some studies report no association between cholesterol measured in later life and incidence of dementia (Li et al., 2005; Tan et al., 2003); whereas others find that lower levels of cholesterol are associated with an increased risk of dementia (Kuusisto et al., 1997; Reitz et al., 2004; Romas et al., 1999; Zuliani et al., 2010) and worse performance on measures of global cognition and processing speed (van den Kommer et al., 2009). Inflammation may account for some of these findings; community-dwelling older adults from the InChianti study who developed dementia within a 3-year

period had lower levels of cholesterol and higher levels of interleukin (IL)-6, a marker of systemic inflammation (Zuliani et al., 2010).

Sex, ethnic, and genetic factors further complicate the picture. In a study of native Africans aged 70 and older living in the US, the prevalence of AD increased with increasing levels of cholesterol (Hall et al., 2006), while ApoE ϵ 4 carriers with lower cholesterol levels showed faster declines in processing speed (Evans et al., 2000). Interesting sex differences were noted in the NHANES III study; low cholesterol was associated with slower visuomotor speed only in young and middle-age men, but not women (Zhang, Muldoon, & McKeown, 2004). In post-menopausal women, those within the highest quartile of cholesterol had the highest odds of cognitive impairment compared to women in the three lowest quartiles (Yaffe, Barrett-Connor, Lin, & Grady, 2002).

High cholesterol levels are related to cardiovascular and cerebrovascular disorders, both of which are independent risk factors of AD, and are a hypothesized mechanism to explain the link between cholesterol levels and cognitive function. Although, Solomon et al. (2009) found a relationship between cholesterol levels and dementia even after controlling for several vascular risk factors, suggesting that other mechanisms might explain the association. In addition, mechanisms that account for low cholesterol levels in those with dementia still need to be further explored. Low levels of cholesterol are a risk factor for atherosclerosis (Duron & Hanon, 2008) and stroke (MacMahon et al., 1990), which have been associated with dementia. Systemic inflammation, overall poor health associated with dementia, and survivor bias may explain these findings (Zuliani et al., 2010).

Animal studies with obese rats suggest that elevated triglycerides disrupt leptin transport across the blood-brain barrier (BBB; Banks et al., 2004). Leptin, a hormone produced by adipose tissue which regulates appetite and metabolism, is beneficial to brain regions important for memory function, including the hippocampus (Banks, 2008; Harvey, Solovyoa, & Irving, 2006). During times of both starvation and obesity triglycerides increase in the blood. As a result, levels of leptin in the blood decrease and BBB transport is inhibited by triglycerides. This signals the brain to redirect calories from “non-essential” activities, like immune function and cognition, to essential activities, like appetite, necessary for survival (Banks, 2008). Leptin has been implicated in AD pathogenesis. In obese, but otherwise healthy individuals, leptin transport across the BBB is significantly impaired affecting A β production (Elmqvist & Flier, 2004). In addition, evidence suggested that A β is associated with inflammatory biomarkers (C-reactive protein) and high levels of HDL cholesterol. This implicates proteins associated with inflammation, cardiovascular disease, and diabetes in the association between BMI and A β levels (Balakrishnan et al., 2005). High expression of amyloid precursor protein (APP) is found in adipose tissues, and is up-regulated in obese people which is linked to insulin resistance and hyperinsulinemia (Lee, Martin, Maple, Tharp, & Pratley, 2009). APP is also important for synapse formation and neural plasticity and is the primary component of amyloid plaques found in AD (Priller et al., 2006).

Diabetes Mellitus

Insulin is critical for regulating carbohydrate and fat metabolism in the body as well as regulating brain and cognitive functions. Insulin resistance develops when the body does not effectively use insulin which can lead to Type 2 DM. In epidemiological

studies, DM is a risk factor for all types of dementia and is a relatively common chronic disease that affects about 8% of the total US population (CDC, 2005) and over 25% of adults over the age of 60 (Kirkman et al., 2012). The vast surge in the number of individuals with Type 2 DM is clearly linked with increasing rates of overweight and obesity. Older adults have a high risk of developing Type 2 DM due to the effects of increasing insulin resistance and impaired islet functioning associated with aging (Kirkman et al., 2012). Diabetes negatively affects certain cognitive abilities and these deficits being to appear in the very early stages of the disease (Ruis et al., 2009). Cognitive performance in those with diabetes declines 20% to 70% faster than those without the disorder (Strachan, Price, & Frier, 2008). Specifically, cognitively healthy older adults with DM showed faster declines in attention, psychomotor speed, and short-term memory compared to those in other glucose metabolism groups (i.e., normal or impaired fasting glucose); effects did not attenuate after adjustment for other vascular risk factors (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001). The most recent meta-analysis of Type 2 DM and dementia risk, which pooled data from 19 studies with over 40,000 individuals, reported a combined overall relative risk (RR) for dementia of 1.51 (95% CI 1.31-1.74). When specific dementia diagnoses were analyzed the RR for VaD was stronger (RR=2.48; 95% CI 2.08-2.96) compared to AD (RR=1.46; 95% CI 1.20-1.77; Cheng et al., 2012). Diabetes may also accelerate conversion from MCI to dementia. In people with MCI, diabetes was associated with a 1.5 – 3 times higher conversion rate to dementia (Li et al., 2011; Xu et al., 2010).

Unlike blood pressure and cholesterol, in which there is a non-linear relationship with cognitive performance that appears to change with age, DM negatively affects

cognition across the life span. Duration of the disease is an important determinate of the magnitude of the impact of DM on cognition. A case-control population-based study suggested that earlier onset, longer duration, and greater severity of DM was more important when exploring the association between MCI and DM. MCI was associated with an onset of DM prior to age 65 (OR = 2.20, 95% CI: 1.29-3.73), DM duration greater than 10 years (OR = 1.76, 95% CI: 1.16-2.68), and the presence of DM-related complications (OR = 1.80, 95% CI 1.13-2.89) even after adjusting for age, sex, and education (Roberts et al., 2008).

Structural changes in the brain have also been linked to diabetes. Insulin at optimal doses with adequate glucose availability facilitates memory. However, when there is an imbalance of glucose availability, glucose metabolism issues can occur. AD has often been referred to as “type 3 diabetes” because insulin signaling is impaired and is associated with an accumulation of A β and tau proteins. Increased insulin resistance and diabetes have been associated with hippocampal atrophy as well decreased cerebral blood glucose levels (Bourdel-Marchasson et al., 2010). Structural and functional neuroimaging studies find that individuals with Type 2 DM have reduced gray matter and glucose metabolism in fronto-temporal brain regions (García-Casares et al., 2014). These abnormalities may underlie the transition to MCI in persons with Type 2 DM. Compared to older adults without Type 2 DM, individuals with Type 2 DM (both with and without MCI) showed decreased total gray matter volume. Significant differences were also observed in the temporal, frontal, and occipital lobes when Type 2 DM individuals were compared to healthy controls (Zhang et al., 2014).

Several pathological mechanisms are thought to explain the link between DM and dementia. One possible mechanism comes from studies which report DM was associated with brain infarcts and changes in microvasculature (Peila, White, Masaki, Petrovitch, & Launer, 2006). In addition, DM could cause dementia indirectly through cerebrovascular disease (Kimm et al., 2011). Insulin resistance has been implicated in AD (Kuusisto et al., 1997; Morris et al., 2014). Impaired insulin secretion, glucose intolerance, and insulin resistance were associated with an increased risk of AD 35 years later after adjusting for several confounders (Rönnemaa et al., 2008). Morris and colleagues (2014) compared insulin resistance in aging and age-related neurodegenerative disorders (i.e., AD, Parkinson's disease, and cognitively healthy older adults). They found that insulin resistance was increased in individuals with AD and Parkinson's and was associated with reduced gray matter volume in multiple regions including the PFC, hippocampus and the temporal and parietal lobes (Morris et al., 2014). Hyperglycemia (high blood sugar), a symptom of diabetes, can lead to increased oxidative stress. The constant production of free radicals, a product of oxidative stress, places a huge burden on an individual's body. Indeed, both hypo- and hyper-glycemia negatively affect multiple cognitive domains including memory, psychomotor speed, attention, and executive functioning (Brands, Kessels, deHaan, Kappelle, & Biessels, 2004).

Systemic Inflammation - A Common Link

Obesity is often characterized as a low-grade, chronic systemic inflammatory condition commonly caused by excess consumption of nutrients and is distinct from classical inflammation due to infection, pain, or heat which is acute in nature and only occurs at the site of the injury. Inflammation in adipose tissue can lead to insulin

resistance in adipocytes through a number of inhibitory signal pathways. The effects of inflammation on adipose tissue are complex but all appear to alter the normal adipocyte processes and active stress responses (Gregor & Hotamisligil, 2011).

The immune system's inflammatory response has also been implicated in AD and is a hallmark of hypertension, hyperlipidemia, and DM. The risk of developing many disorders, including diabetes and atherosclerosis, is significantly increased with high levels of inflammation (Yaffe et al., 2004). Pro-inflammatory cytokines, like IL-6 and tumor-necrosis factor- α , as well as C-reactive protein, are associated with systemic inflammation and increased susceptibility to illness and infection. These inflammatory factors have been associated with diabetes and vascular risk factors of AD (Haan, 2006). After five years of follow-up, individuals with metabolic syndrome and high levels of inflammation had a higher risk of cognitive impairment compared to those without metabolic syndrome (RR = 1.66, 95% CI: 1.19-2.32; Yaffe et al., 2004).

Metabolic syndrome is a cluster of associated cardiovascular risk factors including obesity, hypertension, hypercholesterolemia, and impaired glucose tolerance (NCEP, 2001), thought to negatively affect cognition. There is controversy surrounding this construct and many have argued that the metabolic syndrome offers little additional prediction of negative health events and mortality beyond its components (Khoshdel, Carney, & Gillies, 2012). Although definitions of metabolic syndrome have changed many times over the last 40 years, all have included some measure of impaired glucose metabolism, elevated blood pressure and triglycerides, and central obesity (Snow, 2010). Complications associated with metabolic syndrome (e.g., atherosclerosis, heart attack, stroke, Type 2 diabetes) are associated with impaired cognitive functioning (Duron &

Hanon, 2008; Hughes & Ganguli, 2009; Kimm et al., 2011). Metabolic syndrome may increase dementia risk because it summarizes the joint effects of these risk factors.

In a sample of well-educated middle-aged and older adults, those with metabolic syndrome had a significantly lower IQ compared to those without the diagnosis (Hassenstab, Sweat, Bruehl, & Convit, 2010). Large negative effects on cognition were noted in areas of learning and recall ($\eta_p^2 = 0.12$). These results are especially striking because lower education is often associated with metabolic syndrome, as well as an increased risk of dementia, and this sample contained only well-educated adults. By removing educational attainment as a possible explanation for the differences in cognition, it suggests that metabolic syndrome itself, and not education, is associated with cognitive impairments (Hassenstab et al., 2010).

Several conclusions can be drawn regarding the mechanisms linking obesity with cognitive function. Perhaps most important is the fact that the described mechanisms are strongly influenced by age and measurement timing. For instance, diagnosis of hypertension or diabetes prior to age 65 appears to confer greater risk for cognitive impairments and/or dementia when compared to a diagnosis after age 65. Age-related normative changes in blood pressure and cholesterol levels may explain the age-dependent relationship between these disorders and cognition. A review of research on cholesterol and later-life cognitive function reported that cholesterol levels decrease with increasing age (van Vliet, 2012). Furthermore, a natural consequence of aging is the elongation of cerebral vessels. Higher blood pressure in late life ensures adequate perfusion of white matter. (Cherubini et al., 2010).

Regions of the brain that are particularly vulnerable to age, including the PFC, hippocampus, and the temporal and parietal lobes, are also vulnerable to the negative effects of conditions associated with metabolic syndrome. Of particular importance, areas of the brain that are less vulnerable to age, like the supplementary motor areas, and thalamus, are negatively affected by hypertension (Gąsecki et al., 2013).

Furthermore, none of these diseases operate in isolation. Comorbidities which become more prevalent with age, have profound effects on an individual's ability to self-care and are important in obesity, disability, and cognition. Substantial evidence implicates obesity as a major cause of comorbidities which can lead to functional impairments (Ackerman & Osborne, 2012; Al Snih et al., 2007; Alley & Chang, 2007; Backholer et al., 2011; CMMS, 2012; Ferraro et al., 2002; Friedman et al., 2001).

Cross-sectional studies report that the number of chronic conditions increases the risk of difficulties in ADLs (Guralnik, LaCroix, Everett, & Kover, 1989), IADLs (Fried, 1996), and mobility disability (Verbugge, Lepkowski, & Imanaka, 1989) in a linear fashion. In fact, the presence of a single chronic condition was a significant predictor of functional declines (Guralnik et al., 1993). Given that 82% of Medicare beneficiaries aged 65 and older had one or more chronic conditions in 1999 (Wolff, Starfield, & Anderson, 2002) and in 2010 almost 53% had at least three chronic conditions (CMMS, 2012), disability is a major concern for older adults. Healthcare costs of people with difficulties in 5-6 ADLs are almost 30-times higher than those with no ADL difficulty. This number dramatically increases in individuals with both cognitive impairment and disability; healthcare costs have been estimated to be over 50-times greater in these individuals (Taylor et al., 2001).

In summary, considerable research is still needed to elucidate the mechanisms by which obesity is associated with cognitive impairments and dementia risk. To date, there is considerable evidence for increased dementia risk and specific cognitive impairments in obese persons. The cause of obesity-related cognitive dysfunction is difficult to establish because of the prevalence of comorbidities (diabetes, hypertension), each of which influence cognitive functioning. Longitudinal studies are needed to investigate the pathophysiological mechanisms which lead to cognitive- and brain-related changes associated with obesity.

Chapter 3. Dynamic Relationship between Longitudinal BMI and Cognition

Obesity is often referred to as one of the most serious health problems of the 21st century (Barness, Opitz, & Gilbert-Barness, 2007), accounting for an estimated 400,000 deaths each year in the US (Mokdad, Marks, Stroup, & Gerberding, 2004), and has serious implications for an aging population. In fact, obesity is the second leading cause of preventable death in the US (Ogden, Carroll, McDowell, & Flegal, 2007).

Studies of obesity and cognition in children and adolescents provide substantial evidence that obesity is associated with impaired cognitive functioning, independent of cardiovascular and socioeconomic risk factors (Smith et al., 2011). One of the most consistent findings in obese children and adolescents are deficits in executive function, followed by deficits in short-term memory, global cognition, and verbal abilities when compared to their normal weight peers (Krombholz, 2013; Smith et al., 2011). Some research suggests that executive dysfunction is a risk factor for increased body mass index (BMI) which may induce a bidirectional relationship between obesity and cognitive performance. One longitudinal study found that poor executive function at age 4 predicted a high BMI at age 6 (Guxens et al., 2009); whereas another study followed around 8,000 individuals from age 7 to age 33 and found that poor hand control and coordination at age 7 predicted obesity at age 33 even after taking into account multiple confounders (Osika & Montgomery, 2008). Aspects of executive functioning may have a direct effect on self-monitoring and goal-directed behavior which are necessary to monitor and maintain energy balance. If this is true, normative age-related declines in executive function may help explain why the prevalence of overweight and obesity

increases dramatically in later life (Ogden et al., 2007; Salthouse, Atkinson, & Berish, 2003).

A consistent finding across multiple studies is the u-shaped association between BMI and dementia risk (Anstey et al, 2011; Beyound, Beyound, & Wang, 2008; Fitzpatrick et al., 2009; Gustafson, 2006, 2008; Hassing et al., 2010; Kivipelto et al., 2005; Kuo et al., 2006; Sabia et al., 2009; Smith et al., 2011; Stewart et al., 2005), where both low and high BMI increase risk of dementia. Higher BMIs have been associated with an increased risk of chronic conditions like hypertension and diabetes, both of which are independently associated with an increased risk of cognitive decline and Alzheimer's disease; while lower BMIs have been associated with wasting diseases and frailty (Fulop et al., 2010; Gill et al., 2002). The picture becomes less clear when examining the association between BMI and cognitive functioning in later life. Low (Green et al., 1994; Buchman, Wilson, Bienias, Shah, Evans, & Bennet, 2005) and high BMI (Corley, Gow, Starr, & Deary, 2010; Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003, 2005; Kuo et al., 2006) as well as weight loss (Bagger, Tanko, Alexandersen, Qin, & Christiansen, 2004; Bruhbacker, Monsch, & Stähelin, 2004; Buchman et al., 2005) and weight gain (Bagger et al., 2004) have been associated with lower cognitive scores.

Although evidence supports a u-shaped association between BMI and dementia risk, less is known about concurrent trajectories of BMI and cognitive performance. The goal of the current study was to investigate the dynamic longitudinal relationship between cognitive performance and BMI among older adult participants of the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial. Specifically, over a 10-year period we sought to: 1) determine whether baseline cognitive performance is

associated with changes in BMI; 2) determine whether baseline BMI was associated with changes in cognitive performance; and 3) examine if change in cognitive performance is associated with longitudinal changes in BMI.

Methods

The ACTIVE trial is a randomized, controlled trial designed to evaluate the effectiveness of three cognitive training interventions (i.e., memory, reasoning, and processing speed) on cognitive abilities and functioning of independently-living cognitively healthy older adults. Details on the screening, eligibility criteria, and recruitment have been previously reported in the literature (Ball et al., 2002; Jobe et al., 2001). Persons were excluded if they 1) had a Mini-Mental State Exam (MMSE) score of <22; 2) had a diagnosis of Alzheimer's disease; 3) were functionally impaired, (requiring assistance in dressing, personal hygiene, or bathing three or more times in the prior week); 4) had medical conditions that would predispose them to imminent functional decline (e.g., stroke within the last year, certain cancers); 5) previously participated in cognitive training interventions; 6) or had vision, hearing, or communication impairments.

ACTIVE recruited 2,832 participants in 1998, of whom 2,802 were randomized to one of four groups: 1) memory training (n=703); 2) reasoning training (n=699); 3) processing speed training (n=702); or 4) a no-contact control (n=698). At baseline participants were between 65-94 years of age and 73% of the sample reported White race (African American 26%). The sample was re-contacted for subsequent follow-up immediately following the intervention (post-test) and during the years of 1999-2001 (1st

annual), 2000-2002 (2nd annual), 2001-2002 (3rd annual), 2003-2004 (5th annual), and 2008-2009 (10th annual).

The current study analyzed the association between body weight and cognitive function over 10 years in ACTIVE participants.

Measures

Classification of Body Weight. Body weight status was classified based on body mass index (BMI), a measure of weight adjusted by height. BMI was not measured at post-test or the first annual follow-up in the ACTIVE study.

Cognitive Function

Trained assessors administered the test battery, which included a global cognitive measure and standardized neuropsychological tests to evaluate memory, reasoning, and processing speed. Each primary outcome was standardized to its baseline values. A composite measure of performance was computed for each of the three cognitive domains targeted by an ACTIVE intervention arm (i.e., memory, reasoning, processing speed), by equally weighting each measure within that domain, pooling total scores, and performing a Blom transformation (Blom, 1958) to normalize distributions. Following transformation, distributions of outcomes were normal. Test scores were then summed to form baseline cognitive composite scores that were standardized to the mean and standard deviation of the entire sample. If one or more tests of a composite measure were missing, the composite score was calculated as the average of the non-missing tests.

Memory. A memory composite score was created using the Rivermead Behavioral Memory Test (RBMT) Paragraph Recall test and modified versions of the Hopkins

Verbal Learning Test (HVLТ) and the Rey Auditory Verbal Learning Test (AVLT). These measures include an immediate learning component. To reduce practice effects, the ACTIVE study design used parallel, but not equivalent forms of the memory tests at each visit. When alternate forms are not of equivalent difficulty, analyses of intra-individual changes may be unintentionally biased (Gross et al., 2012). Alternate forms were placed on an equivalent metric using equipercentile equating procedures (Kolen & Brennan, 1995). A higher memory composite score indicated better memory function.

Reasoning. For the reasoning composite three tests, Word Series (Gonda & Schaie, 1985), Letter Series (Thurstone & Thurstone, 1949), and Letter Sets (Erkstrom, French, Harman, & Dermen, 1976) were used. Word Series and Letter Series require participants to identify a pattern in a set of words or letters, and then select the next stimulus in the series from a list of possible answers. The Letter Set task requires participants to identify a common rule among four to five letter sets, marking the set that does not follow the rule. A higher reasoning composite score indicated better performance.

Processing Speed. The processing speed composite score was derived from four Useful Field of View (UFOV) tasks. The UFOV is a measure of information processing speed and selective and divided attention, and is related to IADLs and indices of mobility (Edwards et al., 2009). The test is administered on a touch-screen computer and consists of four increasingly complex subtests composed of multiple trials that vary in duration from 17 to 500ms. Lower scores on the UFOV indicated better performance.

Digit Symbol Substitution Task. The Digit Symbol Substitution Test (DSST) is a subtest of the Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981) and is

sensitive to virtually all neurocognitive impairments and depression (Dickinson, Ramsey, & Gold, 2007). A key at the top of the form pairs a number (1-9) with a symbol. The form consists of boxes of numbers with an empty space below to fill in the corresponding symbol. Participants are given 90 seconds to fill in corresponding symbols under the number boxes.

Other Covariates

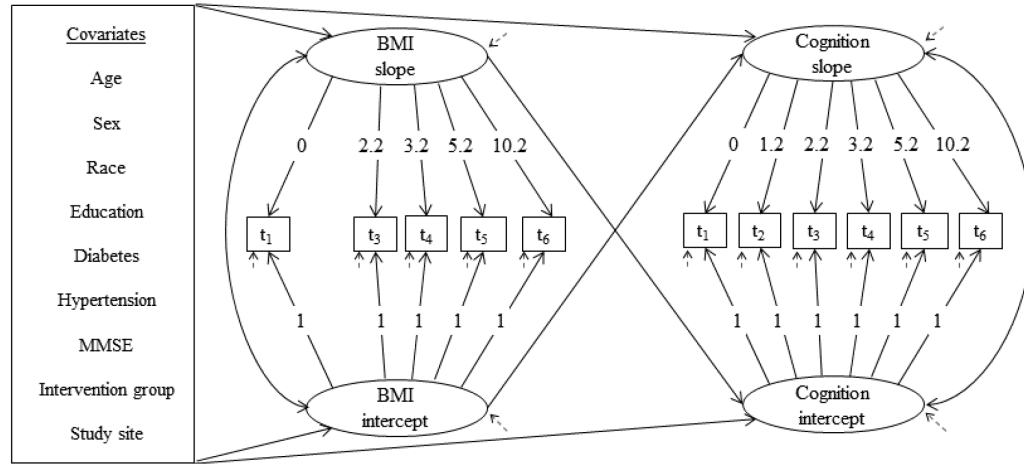
Self-reported history of diabetes or hypertension at baseline were included as covariates because of their known association with both BMI and cognitive performance (Gąsecki, Kwarciany, Nyka, & Markiewicz, 2013; Kirkman et al., 2012; Kuo et al., 2005). Other covariates included age (in years), sex, race (White vs. African American), years of education, baseline MMSE score, intervention group, and study site.

Analysis

Differences in baseline characteristics by BMI categories were assessed by one-way analyses of variance or χ^2 tests when appropriate. Age and education were mean-centered for all analyses (M=73.6 and 13.5, respectively). All cognitive outcomes were standardized (M=50, SD=10) before fitting latent growth curve models. A series of models were estimated to investigate the longitudinal relationship between cognitive performance and BMI across the baseline, 1-, 2-, 3-, 5-, and 10-year visits. First, unconditional latent growth curve models (LGCM) were initially fit to each cognitive outcome (i.e., memory, reasoning and processing speed) and BMI using Mplus 7 (Muthén & Muthén, 2012). Next, a parallel process growth model was used to estimate the association between the growth parameters (i.e., latent intercepts and slopes) of the

cognitive outcomes and BMI (Figure 2) and included age, sex, race, years of education, history of diabetes or hypertension, baseline MMSE, intervention group, study site, and retest effects as covariates. Parallel process growth models are a type of latent growth curve model used to investigate change over time and explore predictors of these changes. Specifically, parallel process growth models allow the growth curves of BMI and cognition to be modeled simultaneously. The factor loadings on the growth rate factor are specified to reflect the time intervals between measurements and the growth trajectory shape. Setting the loadings as 0, 1.2, 2.2, 3.2, 5.2, and 10.2 reflects the linear trajectory across six time points at unequal intervals. The intercept and slope of BMI was allowed to correlate with the corresponding intercept and slope for each cognitive outcome. This allowed for the examination of both cross-sectional associations between BMI and cognitive outcomes, in addition to examining the extent to which changes in BMI were associated with changes in cognition over a 10-year period. Model fit was determined using the root mean square error of approximation (RMSEA), comparative fit index (CFI), and the standardized root mean square residual (SRMR). An RMSEA <0.05 , a CFI >0.96 , and a SRMR <0.08 indicate excellent model fit (Wu, West, & Taylor, 2009). After the final model was selected, sensitivity analyses were conducted. For each of the four cognitive outcomes, multiple group models were run to test for invariance of associations by intervention group. There were no significant differences by intervention arm; however, all models included intervention group as a covariate.

Figure 2. Parallel process latent growth model of BMI and cognitive performance



Legend. Parallel process latent growth curve model of BMI and cognitive performance. Latent variable intercepts and slopes are regressed on covariates that include age, sex, race, years of education, history of diabetes or hypertension, baseline MMSE score, intervention group, and study site. Residual error variances are shown by smaller dashed arrows going towards the observed (boxed) and latent (circled) dependent variables. Numbers on arrows going from latent growth parameters to observed time points indicate factor loadings. T = Assessment wave (1=Baseline; 2=Year 1; 3=Year 2; 4=Year 3; 5=Year 5 6=Year 10).

Results

Exploratory analyses revealed all outcome measures were approximately normally distributed. Participant characteristics as a function of BMI categories are presented in Table 5. Persons who were classified as Class II obese ($\text{BMI} \geq 40\text{kg/m}^2$) at baseline were more likely to be younger, female, have fewer years of education, more self-reported health conditions, and lower scores on the MMSE. Participants classified as under- ($\text{BMI} < 20\text{kg/m}^2$) or normal-weight ($\text{BMI} 20\text{-}24.9\text{kg/m}^2$) were more likely to be older, female, and White with an average of 2 chronic health conditions. At baseline, the memory and reasoning composite scores did not significantly differ by BMI categories, while under- and normal-weight participants had significantly slower times on the speed composite. These results replicate findings from Kuo and colleagues (2006) which

analyzed baseline association between BMI and cognitive performance in the ACTIVE study.

Prior to fitting a parallel process parallel process growth model, LGCM were fit for each cognitive outcome. The memory LGCM was an acceptable fit for the data, CFI=0.99, RMSEA=0.03, SRMR=0.02. The LGCMs also provided acceptable fit for the reasoning (CFI=0.98, RMSEA=0.04, SRMR=0.03) and speed (CFI=0.97, RMSEA=0.04, SRMR=0.05) composite scores and the DSST (CFI=0.99; RMSEA=0.03; SRMR=0.03) data. As a next step, unadjusted parallel process growth models were fit for each cognitive outcome (Table 6). Finally, a parallel process growth model adjusted for age, sex, race, years of education, history of diabetes or hypertension, intervention group, study site, and re-test effects was fit to each cognitive outcome (Table 7).

For each cognitive outcome, standardized regression coefficients describing the association between covariates and intercepts and slopes are presented (Table 7) before describing the relationships between cognitive performance and BMI.

Memory. At baseline, older age ($\beta = -0.21$), male sex ($\beta = -0.08$), White race ($\beta = -0.15$), greater educational attainment ($\beta = -0.16$), and higher MMSE scores ($\beta = -0.07$) were associated with lower BMI, whereas a history of diabetes ($\beta = 0.21$) or hypertension ($\beta = 0.18$) was associated with a higher BMI. Older age ($\beta = -0.39$), male sex ($\beta = -0.14$), and a history of diabetes or hypertension ($\beta = -0.07$; $\beta = -0.05$; respectively) were associated with lower memory composite scores, whereas individuals who indicated White race ($\beta = 0.21$), more years of education ($\beta = 0.31$), and higher MMSE scores ($\beta = 0.52$) had higher memory composite scores. Age was associated with rate of change over time, such that older individuals had steeper annual rates of weight loss ($\beta = -0.10$) and

decline on the memory composite ($\beta = -0.30$). Race was associated with a steeper annual rate of change on the memory composite score ($\beta = -0.13$).

Reasoning. At baseline, older age ($\beta = -0.21$), male sex ($\beta = -0.07$), White race ($\beta = -0.15$), greater educational attainment ($\beta = -0.13$), and higher MMSE scores ($\beta = -0.05$) were associated with a lower BMI, while a history of diabetes or hypertension ($\beta = 0.22$; $\beta = 0.18$; respectively) were associated with a higher BMI. Older age ($\beta = -0.32$) and history of diabetes or hypertension ($\beta = -0.06$, $\beta = -0.08$; respectively) were associated with worse performance on the reasoning composite, whereas White race ($\beta = 0.31$), male sex ($\beta = 0.06$), greater educational attainment ($\beta = 0.43$) and higher MMSE scores ($\beta = 0.52$) were associated with better performance. Older age was associated with rate of change over time such that older individuals had steeper annual rates of decline in BMI and reasoning performance over time ($\beta = -0.13$; $\beta = -0.23$, respectively). Educational attainment was associated with rate of change over time such that individuals with greater educational attainment had faster rates of decline on the reasoning composite ($\beta = -0.11$).

Speed. At baseline, older age ($\beta = -0.19$), male sex ($\beta = -0.09$), White race ($\beta = -0.16$), greater educational attainment ($\beta = -0.17$) and higher MMSE scores ($\beta = -0.09$) were associated with lower BMI, while history of diabetes or hypertension ($\beta = 0.21$, $\beta = 0.18$; respectively) were associated with higher BMI. Individuals at baseline who were older ($\beta = 0.50$) and had a history of diabetes or hypertension ($\beta = 0.08$; $\beta = 0.05$; respectively) had slower speed scores. Individuals at baseline who were male ($\beta = -0.06$), White ($\beta = -0.10$), had greater educational attainment ($\beta = -0.20$), and higher MMSE scores ($\beta = -0.36$) had faster speed scores. Only older age ($\beta = -0.15$) and history of hypertension ($\beta = -0.08$) were associated accelerated declines in BMI over time.

DSST. At baseline, older age ($\beta = -0.22$), male sex ($\beta = -0.07$), White race ($\beta = -0.15$), greater educational attainment ($\beta = -0.15$), and higher MMSE scores ($\beta = -0.06$) were associated with lower BMI, while diabetes ($\beta = 0.21$) and hypertension ($\beta = 0.14$) were associated with higher BMI. Individuals at baseline who were older ($\beta = -0.30$), male ($\beta = -0.09$), and reported a history of diabetes ($\beta = -0.10$) or hypertension ($\beta = -0.06$) had lower scores on the *DSST*, while individuals who were White ($\beta = 0.26$), had greater educational attainment ($\beta = 0.28$) and higher MMSE scores ($\beta = 0.40$) had higher scores on the *DSST*. Age ($\beta = -0.13$) and history of hypertension ($\beta = -0.10$) were associated with rate of change in BMI over time, such that older individuals and those with a history of hypertension had faster rates of change in BMI over time. Age ($\beta = -0.25$), race ($\beta = -0.13$), and history of diabetes ($\beta = -0.11$) were associated with rate over change over time in *DSST* scores, such that older individuals and those with a history of diabetes had steeper declines in *DSST* over time.

Next, a parallel process GMM was fit to estimate the association between growth parameters of each cognitive outcome and BMI. Findings suggest that on average, participants were overweight (BMI 28.7 kg/m²) at baseline and lost about 0.1 kg/m² annually (roughly 2.2 pounds over 10 years). Better baseline memory ($\beta=0.07$, SE=0.04, $p=.04$), reasoning ($\beta=0.08$, SE= 0.03, $p=.02$), speed ($\beta=-0.16$, SE= 0.04, $p=.007$), and *DSST* ($\beta = 0.09$, SE=0.04, $p=.01$) performance was associated with attenuated declines in BMI (Table 7). Higher baseline BMI was associated with faster processing speed performance at baseline ($\beta= -0.08$, SE=0.02, $p<.0001$) and attenuated declines in reasoning ability ($\beta=0.10$, SE=0.02, $p<.0001$). Interestingly, changes in BMI were associated with changes in memory ($r=0.29$, $p<.0001$), reasoning ($r=0.29$, $p<.0001$),

processing speed ($r = -0.35, p < .0001$), and DSST ($r = 0.25, p < .0001$) over 10 years after adjusting for demographic and health characteristics suggesting that slower cognitive decline is associated with slower declines in BMI.

Discussion

The use of parallel process growth models in the current study simultaneously analyzed trajectories of BMI and cognitive performance to examine the dynamic relationship between these two processes. Current findings highlight the complex relationship between cognitive performance and BMI in older adults. Higher scores at baseline on the memory and reasoning composites were associated with steeper declines in BMI, while faster baseline processing speed scores were associated with slower rates of decline in BMI. Higher BMI at baseline was associated with better initial processing speed performance (Kuo et al., 2006) and accelerated improvement in reasoning ability which replicates prior cross-sectional analyses using ACTIVE data. Current findings raise the possibility that obesity produces differential effects on memory, reasoning, and processing speed and may suggest that, in the current sample of older adults, individuals with higher cognitive scores at baseline lost weight at a slower rate compared to those with lower cognitive scores.

Interestingly, changes in BMI were associated with changes in memory, reasoning, and processing speed. Findings suggest that slower cognitive decline is associated with greater increase in BMI over time. Based on prior analyses (results not shown), attrition over the 10-year study period was related to baseline cognitive performance such that individuals with lower cognitive scores were more likely to drop out; however, baseline BMI was not associated with attrition. The research exploring the

link between changes in weight and cognitive performance is mixed. Results from community-dwelling Korean older adults aged 60-85 complement findings in the ACTIVE study (Han et al., 2009). Increased adiposity in men who were obese (as measured by BMI, waist circumference (WC), and waist-hip ratio (WHR)) at baseline was associated with a positive change in cognitive functioning. For women, both decreased adiposity over time when obese at the baseline (measured with WHR), or increased adiposity in women with normal adiposity at baseline (measured with WC), were both associated with cognitive declines. In contrast, results from a sample of middle-aged and older Australian women found no association between changes in weight and changes in cognitive performance (Lo et al., 2012). Null findings could be explained by modest sample size (n=334), lack of control for practice effects on the cognitive measures or the fact that participants were seen at only 2 occasions, roughly 7.5 years apart. These conflicting results highlight the importance of both the age at which adiposity is measured as well as the measurement type.

Recent studies indicate that weight change, not BMI per se, may be more closely linked to cognitive performance in older adults. Findings from the Women's Health Initiative Study of Cognitive Aging (WHISCA) suggested that only weight loss was associated with impaired cognitive scores (i.e., verbal memory, fine motor speed, and global cognitive function; Driscoll et al., 2011) in contrast to results from current analyses in the ACTIVE cohort. Dementia is known to have a long prodromal phase in which appetite is severely decreased leading to significant weight loss and under nutrition (Albanese et al., 2013), explaining why cognitive performance may be associated with future changes in weight. In a postmortem study, dementia neuropathology was inversely

related to BMI (Buchman, Schneider, Wilson, Bienias, & Bennett, 2006) and could explain involuntary weight loss in preclinical dementia. This suggests that the timing of BMI measurement is very important and may determine the relationship between BMI and cognitive performance. Current findings raise the possibility that body weight (BMI) measured in the mid-70s (mean age of ACTIVE participants at baseline 73.6 years) may influence both concurrent and future cognitive performance up to 10 years later in a sample of older adults who were cognitively healthy and independently-functioning at baseline.

Current analyses revealed that higher BMI at baseline was associated with attenuated declines in reasoning, which has been replicated in other samples of older adults (Luchsinger et al., 2013; Sturman et al., 2008). One of the single largest factors that determines whether an individual practices healthy behaviors is intelligence (Gottfredson, 2004). Individuals with higher cognitive abilities may have a reduced risk of obesity because they are more likely to engage in healthy behaviors (e.g., eat a healthier diet, exercise, and regular trips to the doctor).

The current findings must be presented alongside some limitations. First, the ACTIVE trial recruited cognitively healthy and functionally independent older adults at baseline. Due to volunteer bias, the current findings may not generalize to a larger population of older adults. Second, the current study only included a single measure of body composition (BMI) measured in later life. Waist circumference and waist-to-hip ratio are more strongly associated with negative health outcomes compared to BMI (Dagenais et al., 2005; Lindqvist et al., 2006) and differential results by type of body mass measure have been noted (Han et al., 2009). There was no information available on

adiposity parameters in midlife or intentionality of weight loss. Midlife obesity has been linked with an increased risk of cognitive decline and dementia (Anstey et al., 2011; Loeff & Walach, 2013). Dieting has been associated with impairments in reaction time, sustained attention, verbal memory, and working memory capacity (Green & Rogers, 1997;; Kemps, Tiggeman, & Marshall, 2005; Kemps & Tiggemann, 2005; Shaw & Tiggeman, 2004). Additional work is needed to clarify the mechanisms responsible for the association between changes in cognitive performance and changes in BMI across middle-age and later life.

Chapter 4. Longitudinal Mediation of Grip Strength on Weight-Related Changes in Cognition

Mobility disability is the most common form of disability in community samples of older adults, has dramatic effects on activities in everyday life (Ebrahim et al., 2000), and is associated with physical, sensory, and cognitive deficits (Anstey et al., 2005). Obesity may be strongly linked with mobility disability because added weight makes it more difficult to navigate the environment. In fact, results from the Health, Aging and Body Composition study suggest higher BMI was associated with increased risk of mobility limitations (Lee et al., 2005). Findings from the Longitudinal Study of Aging (LSOA), a prospective survey of 5,000 community-dwelling older adults aged 70 and older, suggest that the progression of incident disability began with difficulties in walking and was followed by difficulties in bathing, transferring, dressing, toileting, and feeding (Dunlop et al., 1997).

The increasing prevalence of obesity in older adults has a profound impact on disability. During 1988-2004 the likelihood of functional impairment increased over 40% in obese older adults (Alley & Chang, 2007). Consequently, disability rates are predicted to dramatically increase (Sturm et al., 2004). Data from the National Health and Nutrition Examination Survey (NHANES III) highlight this trend; among obese individuals 37% reported disability in 1994, whereas in 2004, 42% reported disability and functional impairments (Alley & Chang, 2007). While obese populations have grown healthier since the 1960s (Gregg et al., 2005), the age of onset of obesity has decreased (Alley & Chang, 2007). This would suggest that although obese populations are living longer, they are experiencing more disability as a result of living longer with the burden of obesity.

A meta-analysis of obesity and mobility disability in older adults reported consistent findings linking high body mass index (BMI; especially those $> 35 \text{ kg/m}^2$) with an increased risk of mobility disability (Vincent et al., 2010). These results were extended to the disability domains of activities of daily living (ADLs) and instrumental activities of daily living (IADLs), in which obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) older adults aged 65 and older had the highest risk of disability compared with normal weight older adults (Larrieu et al., 2004). Similar to the relationship between BMI and dementia risk, the relationship between BMI and physical disability is curvilinear. There is a beneficial effect associated with older adults being slightly overweight (i.e., $\text{BMI} 25.0 - 29.9 \text{ kg/m}^2$; Rejeski et al., 2010); however, once older adults cross the Class II obesity threshold ($\text{BMI} \geq 35 \text{ kg/m}^2$), the risk of physical disability increases significantly (Al Snih et al., 2007; Ferraro, Su, Gretebeck, Black, & Badlay, 2002; Mendes de Leon, Hansberry, Bienias, Morris, & Evans, 2006; Rejeski et al., 2010).

Mobility impairments refer to the lack of muscle strength required to ambulate, lift heavy objects, or grasp items. Handgrip strength is associated with individual differences in cognitive performance in cross-sectional studies (Nourhashémi et al., 2002; Taekema et al., 2012). It has been hypothesized that grip strength and cognition are related due to central nervous system involvement. Measures of grip strength are sensitive to the aging process and have been used as a proxy for the integrity of the central nervous system (Christensen, MacKinnon, Korten, & Jorm, 2001; Salthouse, Hambrick, & McGuthry, 1998). Older adults in the Hispanic Established Population for the Epidemiological Study of the Elderly (H-EPESE) in the lowest handgrip strength quartile had faster declines on the Mini-Mental State Exam compared to those in the

highest quartile; whereas individuals in the highest grip strength quartile maintained a higher level of cognitive functioning (Alfaro-Acha et al., 2006). Importantly, these results suggest that physical declines may precede cognitive declines.

There are multiple pathways through which obesity can increase the risk of disability in older adults. Direct effects include the increased risk of musculoskeletal conditions, like arthritis. In a nationally representative sample, the odds of arthritis and osteoarthritis were seven times higher for obese individuals compared to normal weight individuals. Furthermore, of those with arthritis or osteoarthritis, obese individuals reported more pain and stiffness, poorer function, greater disease severity, and lower health-related quality of life (Ackerman & Osborne, 2012).

Indirect effects result from the increased risk of diabetes and cardiovascular diseases that are associated with obesity as well as disability. Although BMI may not be the best indicator of adiposity in older adults (see Haboubi et al., 1990; Vailas & Nitzke, 1998), a recent study of multiple adiposity measures (i.e., BMI, waist and hip circumference, fat mass, fat-free fat mass, and percentage fat) found that for both men and women, BMI was the single best predictor of multiple types of disability (Wong et al., 2012).

Progressive loss of muscle mass and an increase in fat mass occur in normal aging (Schultz et al., 2002) leading to lower quality muscle that is less capable of generating strength and power for mobility-related tasks (Marks, 2007). Poorer muscle quality and an increase in fat mass can significantly increase the risk of disability in older adults. A meta-analysis of middle-aged and older adults (Backholer et al., 2011) revealed a stepwise increased risk of ADL limitations in individuals who were classified as

overweight or heavier, relative to normal weight individuals. In fact, when compared with normal weight older adults, older obese adults were more likely to report disabilities in multiple domains including ADLs, IADLs, and mobility even after adjustment for sociodemographic characteristics (Larrieu et al., 2004).

The literature is replete with studies of either BMI and muscle strength and their association with cognitive performance, but few studies have examined the longitudinal mediation of grip strength on weight-related changes in cognition. The purpose of the current study is to examine the extent to which grip strength, a proxy for mobility limitations, mediates longitudinal BMI-related changes in cognition using the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) data set.

Methods

The ACTIVE trial is a randomized, controlled-trial of behavioral training interventions (i.e., memory, reasoning, and processing speed) designed to improve cognitive abilities and functioning of independently-living older adults. Details on the screening, eligibility criteria, and recruitment have been previously reported in the literature (Ball et al., 2002; Jobe et al., 2001). Exclusion criteria were: 1) Mini-Mental State Exam (MMSE) score of ≤ 22 ; 2) functional dependence; 3) medical conditions with high risk of functional decline, including dementia diagnosis; 4) previous participation in cognitive training interventions; 5) vision, hearing, or communication impairments.

ACTIVE recruited 2,832 participants in 1998, of whom 2,802 were randomized to one of four groups: 1) memory training (n=703); 2) reasoning training (n=699); 3) processing speed training (n=702); or 4) a no-contact control (n=698). At baseline participants were between 65-94 years of age and 73% of the sample reported White race

(African American 26%). The sample was re-contacted for subsequent follow-up immediately following the intervention (post-test) and again 1-, 2-, 3-, 5-, and 10-years later.

Measures

Cognitive Function

Trained assessors administered the test battery, which included a global cognitive measure (MMSE; Folstein, Folstein, & McHugh, 1975) and standardized neuropsychological tests to evaluate memory, reasoning, and processing speed. Each primary outcome was standardized to its baseline values. A composite measure of performance was computed for each of the three cognitive domains targeted by an ACTIVE intervention arm (i.e., memory, reasoning, processing speed), by equally weighting each measure within that domain, pooling total scores, and performing a Blom transformation (Blom, 1958) to normalize distributions. Following transformation, distributions of outcomes were normal. Test scores were then summed to form baseline cognitive composite scores that were standardized to the mean and standard deviation of the entire sample. If one or more tests of a composite measure were missing, the composite score was calculated as the average of the non-missing tests.

Memory. A memory composite score was created using the Paragraph Recall test from the Rivermead Behavioral Memory Test (Wilson, Cockburn, & Baddeley, 1985) and modified versions of the Hopkins Verbal Learning Test (HVLT; Brandt, 1991) and the Rey Auditory Verbal Learning Test (AVLT; Rey, 1941). These measures include an immediate learning component. To reduce practice effects, the ACTIVE study design

used parallel, but not equivalent forms of the memory tests at each visit. When alternate forms are not of equivalent difficulty, analyses of intra-individual changes may be unintentionally biased (Gross et al., 2012). Alternate forms of the memory tests were placed on an equivalent metric using equipercentile equating procedures (Kolen & Brennan, 1995). A higher memory composite score indicated better memory function.

Reasoning. For the reasoning composite three tests, Word Series (Gonda & Schaie, 1985), Letter Series (Thurstone & Thurstone, 1949), and Letter Sets (Erkstrom, French, Harman, & Dermen, 1976), were used. Word Series and Letter Series require participants to identify a pattern in a set of words or letters, and then select the next stimulus in the series from a list of possible answers. The Letter Set task requires participants to identify a common rule among four to five letter sets, marking the set that does not follow the rule. A higher reasoning composite score indicated better performance.

Processing Speed. The processing speed composite score was derived from subtests of the Useful Field of Task (UFOV). The UFOV is a measure of information processing speed and selective and divided attention, and is related to IADLs and indices of mobility (Edwards et al., 2009). The test is administered on a touch-screen computer and consists of four increasingly complex subtests composed of multiple trials that vary in duration from 17 to 500ms. Lower scores on the UFOV indicated better performance.

The Digit Symbol Substitution Test (DSST) is a subtest of the Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981) and is sensitive to virtually all neurocognitive impairments and depression (Dickinson, Ramsey, & Gold, 2007). A key at the top of the form pairs a number (1-9) with a symbol. The form consists of boxes of

numbers with an empty space below to fill in the corresponding symbol. Participants are given 90 seconds to fill in corresponding symbols under the number boxes.

Physical Health

Body Mass Index. Body weight status was classified based on body mass index (BMI), a measure of weight adjusted by height, and is thought to reflect overall adiposity.

Handgrip Strength. Handgrip strength is a reliable proxy of overall strength and predicts physical disability and mobility limitations (Choquette et al., 2010; Rantanen et al., 1999; Sallinen et al., 2010; Shinkai et al., 2000). Grip strength was measured with the JAMAR® hydraulic hand dynamometer (Lafayette Instruments, Lafayette, Ind., USA).

Two trials, measured in kilograms, are recorded for the dominant hand, defined as the hand used for writing. The highest value of the 2 trials was used in the analyses.

Participants were in a seated position with the elbow flexed at 90° and were instructed to squeeze the handle as hard as possible for 3-5 seconds. Participants who reported recent worsening of pain or arthritis in their wrists, tendonitis, or hand/wrist surgery in the previous 3 months did not complete the grip strength measure. Grip strength was not measured at post-test or the first annual follow-up in the ACTIVE study.

Other Covariates

Women (Fried & Guralnik, 1997), African Americans (Mendes de Leon et al., 2005), and older adults with less education (Mezler, Izmirlian, Leveille, & Guralnik, 2001) have substantially higher rates of mobility disability. Mobility disability is also known to increase dramatically with age and is associated with chronic conditions like diabetes. As such, covariates included age, sex (1=male; 0=female), race (1=White;

0=African American), years of education, baseline MMSE score, history of diabetes and hypertension, study site, and intervention group.

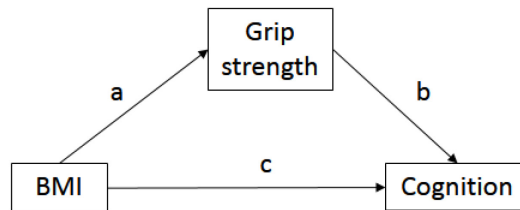
Analysis

Differences in baseline characteristics by sex-specific grip strength tertiles were assessed by one-way analyses of variance or χ^2 tests when appropriate. Age and education were mean-centered for all analyses (M=73.6 and 13.5, respectively). All cognitive and handgrip strength measures were standardized (M=50, SD=10) before fitting latent growth curve models.

A series of latent growth curve models (LGCM) were used to assess changes in handgrip strength and cognition over a 10-year period. Unconditional LGCM were initially fit to grip strength and each cognitive outcome using Mplus 7 (Muthén & Muthén, 2012). Next, a parallel process LGCM was used to model the association between the growth parameters of the cognitive outcomes with grip strength (the mediator). The growth trajectories for grip strength were non-linear which necessitated adding a quadratic function to the growth model. Finally, a model was used to test whether BMI at baseline was related to the latent growth factor of the mediator (path a; see Figure 3), and whether the growth factor of the mediator was related to the growth factor of the outcome, controlling for the BMI path (path b). Mediation is supported when BMI at baseline significantly changes the trajectory of the mediator (grip strength), which, in turn, affects the trajectory of the outcome (i.e., memory, reasoning, processing speed, or Digit Symbol Substitution Task). Bias-corrected bootstrapped confidence intervals (CIs) were used to describe the uncertainty of the mediated effect. The mediated

effect was considered statistically significant if the bias-corrected 95% CIs did not include zero. For bootstrapping, 1,000 replications were used.

Figure 3. Mediating effect of grip strength on cognition



Legend: (a) BMI effect on the mediator; (b) effect of mediator on the outcome variable (c) direct effect of BMI on the outcome variable

For all models, missing data were handled by the maximum likelihood procedure in Mplus 7 (Muthén & Muthén, 2012) which uses all available data and assumes data are missing at random. After the final model was selected, sensitivity analyses were conducted. For each of the four cognitive outcomes, multiple group models were used to test for invariance of associations by intervention group. There were no significant differences by intervention arm; however, all models included intervention group as a covariate. Model fit was determined using the root mean square error of approximation (RMSEA), comparative fit index (CFI), and the standardized root mean square residual (SRMR). An RMSEA <0.05, a CFI > 0.96, and a SRMR <0.08 indicate excellent model fit (Wu, West, & Taylor, 2009).

Results

As a first step, LGCM were fit for each outcome. The LGCM provided acceptable fit for the memory (CFI=0.99, RMSEA=0.03, SRMR=0.02), reasoning (CFI=0.97, RMSEA=0.04, SRMR=0.06), speed (CFI=0.99, RMSEA=0.03, SRMR=0.02), and DSST

(CFI=0.95, RMSEA=0.04, SRMR=0.05) outcomes. For the mediating variable of interest, grip strength, LGCM provided excellent fit (CFI=0.99, RMSEA=0.02; SRMR=0.04). Next, parallel process LGCMs were used to evaluate how baseline BMI affects the growth of the three cognitive outcomes through changing the mediator (grip strength). All models provided good fit, and the RMSEA, CFI, and SRMR were in the acceptable ranges (Table 9).

Participant characteristics as a function of sex-specific tertiles of grip strength are presented in Table 8. At baseline, the number of participants with a history of diabetes or hypertension did not differ by tertiles of sex-specific grip strength. Individuals with higher grip strength values were more likely to be younger ($p<.0001$). For men, there were no significant differences in race by tertiles of handgrip strength, but this was not the case for women. At baseline, White women were more likely to have lower grip strength values compared to African American women ($p<.0001$). This may be explained by the larger proportion of White women with self-reported history of osteoporosis at baseline with lower values on grip strength ($p<.0001$). Higher grip strength values were associated with a higher baseline BMI in both men and women ($p<.0001$, $p=.02$; respectively). Individuals with higher grip strength values at baseline were also more likely to have better scores on the memory, reasoning, and speed composites as well as the Digit Symbol task. However, the magnitude of the effect was larger for men. At baseline, men in the first grip-strength tertile were more likely to have less education ($p=.04$) and lower scores on the MMSE ($p=.02$); this difference was not found for women.

Older individuals were more likely to have both lower grip strength ($\beta=-0.23$; $p<.0001$) and lower cognitive scores ($p<.0001$) at baseline as well as accelerated declines in grip strength ($\beta\approx-0.18$; $p<.0001$; Table 9), memory, ($\beta=-0.38$; $p<.0001$), reasoning ($\beta=-0.25$, $p<.0001$), and speed ($\beta=0.25$, $p<.0001$) scores over time. Compared with women, men were more likely to have better grip strength at baseline ($\beta=0.70$; $p<.0001$) and were more likely to maintain their initial values of grip strength over time as evidenced by attenuated declines over follow-up ($\beta=0.37$; $p<.0001$). Race was associated with baseline cognitive performance and grip strength such that compared with African Americans, Whites had better memory ($\beta=0.21$; $p<.0001$), reasoning ($\beta=0.26$; $p<.0001$), speed ($\beta=-0.12$; $p<.0001$), and DSST ($\beta=0.18$; $p<.0001$) performance. However, Whites on average, had worse grip strength at baseline compared with African Americans ($\beta=-0.20$; $p<.0001$), which may be explained by the higher proportion of White women with a history of osteoporosis.

Individuals with greater educational attainment achieved higher scores on the memory ($\beta=0.20$; $p<.0001$), reasoning ($\beta=0.31$; $p<.0001$), and speed ($\beta=-0.09$; $p<.0001$) at baseline. Greater educational attainment was associated with accelerated declines in reasoning ($\beta=-0.10$; $p=.03$). At baseline, higher MMSE scores were associated with better grip strength ($\beta=0.03$; $p=.05$) as well as better performance on all cognitive measures ($p<.01$). Higher baseline MMSE scores were associated with attenuated declines in speed ($\beta=-0.14$; $p<.01$). Self-reported diagnosis of diabetes was associated with lower grip strength at baseline ($\beta=-0.07$; $p<.0001$), poorer performance at baseline on memory ($\beta=-0.04$; $p=.03$) and speed ($\beta=0.08$; $p<.0001$) measures as well as accelerated declines in memory over time ($\beta=-0.08$; $p=.05$). History of hypertension was not associated with

baseline grip strength or cognitive performance nor associated with changes in these variables over time.

Table 10 shows the results of the mediated effect of BMI on cognition via grip strength. First, for all three outcomes, a higher BMI was significantly associated both with better initial values (i.e., intercept; $\beta=0.08$; $p<.0001$) of grip strength and accelerated declines on grip strength over time ($\beta=-0.05$; $p<.0001$). Second, better grip strength at baseline was associated with slower declines in cognition over time for all cognitive outcomes (memory $\beta=0.21$; reasoning $\beta=0.36$; speed $\beta=-0.21$; and Digit Symbol $\beta=0.21$). Higher BMI at baseline was significantly associated with better reasoning performance at baseline ($\beta=0.04$; 95% CI 0.01, 0.07; $p=.02$) and marginally associated with better speed at baseline ($\beta=-0.04$; 95% CI -0.07, 0.002; $p=.06$). Although there were no direct effects of BMI on cognitive performance, BMI did mediate changes in cognitive performance through its influence on initial levels of grip strength (i.e., intercept) as well as changes in grip strength over time. The indirect effect of BMI on changes in cognition via the grip strength slope was only significant in the memory ($\beta=-0.01$; 95% CI -0.02, -0.004) and reasoning groups ($\beta=-0.04$; 95% CI -0.02, -0.002); marginal significance was achieved in the speed group. BMI also appears to mediate changes in cognition through its influence on initial values of grip strength. Indirect effects of BMI on changes in cognition via the grip strength intercept were significant for the memory ($\beta=0.02$; 95% CI 0.004, 0.03; $p=.02$), reasoning ($\beta=0.03$; 95% CI 0.01, 0.05; $p=.002$), and speed ($\beta=-0.02$; 95% CI -0.03, -0.002; $p=.02$) outcomes.

Figures 4 – 7 illustrate the mediation model, showing the parallel process model for the mediating effect of grip strength on cognition. Statistically significant paths are

shown in bold. The statistically significant paths for the mediating effects are shown with dashed red arrows. For all cognitive outcomes, the initial values of the mediator (grip strength) were significantly and negatively associated with its growth factor ($\beta=-0.59$). This indicates that individuals with higher baseline values of grip strength showed accelerated declines in grip strength over time. Better grip strength at baseline was associated with better baseline performance on the memory ($\beta=0.08, p=.002$), reasoning, ($\beta=0.09, p<.0001$), and speed composites ($\beta=-0.19, p<.0001$). At baseline, individuals with higher reasoning ($\beta=0.09, 95\% \text{ CI } 0.01, 0.17, p=.04$), and DSST ($\beta=0.17, 95\% \text{ CI } 0.03, 0.30, p=.03$) scores showed less decline on grip strength over time.

BMI was significantly positively associated with initial values of grip strength ($\beta=0.08$, all outcomes) and reasoning scores ($\beta=0.04, SE=0.01, p=.01$), and marginally associated with speed ($\beta=-0.04, SE=0.02, p=.06$), suggesting that a higher BMI was associated with better grip strength and reasoning performance as well as faster speed scores. Furthermore, BMI was significantly negatively associated with the grip strength slope (path a; $\beta=-0.05, SE=0.01, p<.0001$), indicating a higher BMI accelerated declines in grip strength. Higher BMI at baseline was also associated with attenuated declines in memory ($\beta=0.30, SE=0.06, p<.0001$) and reasoning ($\beta=0.31, SE=0.01; p<.0001$). For the memory ($\beta=0.24; 95\% \text{ CI } 0.12, 0.36; p<.0001$) and reasoning ($\beta=0.18; 95\% \text{ CI } 0.06, 0.15; p=.003$) outcomes, slower declines in grip strength were significantly associated with slower declines in cognition; (Figure 3, path b). Marginal significance was found for the speed outcome ($\beta=-0.14; 95\% \text{ CI } -0.29, 0.01; p=.06$). Initial levels of grip strength were significantly associated with changes in memory ($\beta=0.21, 95\% \text{ CI } 0.07, 0.35, p=.003$), reasoning ($\beta=0.36, 95\% \text{ CI } 0.23, 0.47, p<.0001$), speed ($\beta=-0.21, 95\% \text{ CI } -0.36,$

-0.05, $p=.008$), and DSST ($\beta=0.21$; 95% CI 0.01, 0.42; $p=.04$) such that better handgrip strength at baseline was associated with attenuated declines in cognition.

Discussion

To our knowledge no study has examined the longitudinal mediating effect of grip strength on cognitive performance in older adults. The current proposal examined whether BMI at baseline affected grip strength and whether the change in grip strength affected measures of cognitive performance over time using mediation analyses. Both higher BMI and better grip strength at baseline were associated with accelerated declines in grip strength over time in all groups. The association between BMI and cognition is often muddied by the inclusion of individuals in a preclinical phase of dementia because individuals often lose weight prior to dementia diagnosis and in the early stages of dementia (Stewart et al., 2005; White, Pieper, & Schmader, 1999). Gao et al. (2011) reported that six years prior to dementia diagnosis, individuals with incident dementia had significantly lower BMI compared to those with normal cognition. Results from the Chicago Health and Aging Project highlight the importance of taking into account dementia diagnosis status of those in a preclinical phase of dementia. When these persons were included, higher BMI was protective against cognitive decline (Sturman et al., 2008).

In the memory and reasoning analyses, the direct effect of grip strength slope was significantly and positively associated with the changes in cognition. Indirect effects from BMI to the memory and reasoning slope via the grip strength slope were also significant but in the opposite direction, suggesting that a higher BMI accelerates declines in grip strength which in turn had a negative effect on cognitive performance. A marginally

significant trend ($p=.08$) in speed composite scores also suggests that BMI had an indirect effect on changes in speed over time through its effects on changes in grip strength.

One of the more provocative findings from the current analyses revealed that initial levels of grip strength were associated with changes in cognition. Better grip strength at baseline was associated with slower declines in memory ($\beta=0.21$; $SE=0.08$; $p=.003$), reasoning ($\beta=0.37$; $SE=0.02$; $p<.0001$), speed ($\beta=-0.21$; $SE=0.06$; $p=.01$) and DSST ($\beta=0.26$; $SE=0.06$; $p=.03$). Several studies have found no association between baseline levels of grip strength and changes in specific cognitive domains (e.g., Christensen et al., 2001; Taekema et al., 2012), whereas others report an association between grip strength and accelerated declines in global cognitive performance (Alfaro-Acha et al., 2006; Clouston et al., 2013; Taekema, Gussekloo, Maier, Westendorp, & de Craen, 2010). Differences in the sampling framework may explain why previous studies did not detect an association between initial levels of grip strength and changes in cognition. Unlike the ACTIVE dataset used in the current analyses, which recruited independently living older adults aged 65 and older at baseline (mean age at baseline was 74 years) with no cognitive or functional impairments, the two previous studies had no exclusion criteria in terms of health or functioning and instead recruited individuals from a general geographic region and/or those who met age requirements. These conflicting results highlight the importance of measurement timing when exploring the complex relationship between functional and cognitive performance.

The current findings suggest that better memory, reasoning, and processing speed are associated with slower declines in handgrip strength over time. This finding has been

replicated in other samples of older adults (Taekema et al., 2012). Others find executive dysfunction is a better predictor of functional decline than age, educational attainment, and general health status (Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000). Executive functioning has also been associated with lower extremity function in several studies of older adults such that individuals with poorer performance on measures of executive function were more likely to have poorer performance on measures of lower extremity function (Ble et al., 2005). A study of twin pairs identified genetic factors common to hand grip strength, processing speed, and working memory (Ogata, Kato, Honda, & Hayakawa, 2014). Previous findings suggest the mechanism driving the association between muscle strength (i.e., grip strength) and cognitive functioning has a neurobiological basis which affects both functional and cognitive decline (Buchman et al., 2007; Raji et al., 2005; Taekema et al., 2012).

Interestingly, in the current analyses grip strength at baseline was associated with baseline memory, reasoning, and speed performance. The reasoning composite score in ACTIVE most closely aligns with executive function in that the three tests used to create the composite score require strategy formation, behavioral spontaneity, and retrieval ability from long-term memory. Although there was no direct effect of the grip strength slope on changes in reasoning performance, there was a direct effect from initial values of grip strength (intercept) on changes in reasoning performance. Furthermore, there were significant effects from BMI to changes in reasoning performance via the grip strength intercept. It is possible that multiple indirect effects with opposing signs can negate the direct effect (MacKinnon, Krull, & Lockwood, 2000).

The current analyses used a well-characterized large sample of older adults followed over a 10-year period. Strengths of the current study include a large, ethnically and geographically diverse sample, single blind multi-site, randomized controlled design, 10 years of follow-up period, multiple measures of cognition and functioning. Each cognitive ability targeted by an intervention (i.e., memory, reasoning, and processing speed) was measured with multiple tests that are known to be sensitive to age-related changes in cognitive abilities. Advanced mediation analysis methods were also used to explore the effect of mediated grip strength on cognition.

When interpreting the current findings, several limitations must be mentioned. First, only one objective measure of physical performance was available in the ACTIVE study. Findings in the literature suggest that measures of physical functioning differ in their sensitivity to cognitive change (Clouston et al., 2013); additional measures of physical performance (e.g., chair stands, gait speed) may have revealed different patterns between BMI, physical functioning, and cognitive performance. There is strong evidence, however, to suggest that grip strength is a valid and reliable marker of physical performance in community-dwelling older adults (see Mijnders et al., 2013; Stevens et al., 2012), predicts physical disability and mobility limitations (Choquette et al., 2010; Rantanen et al., 1999; Sallinen et al., 2010; Shinkai et al., 2000), and is more feasible to administer in clinical and large-scale epidemiological studies. Furthermore, factor analyses comparing handgrip strength and knee extension strength suggest that the two measures reflect a common construct (Bohannon, 2012). Second, although BMI was not associated with attrition over the 10-year study period, attrition was related to baseline

cognitive performance and grip strength such that individuals with better cognitive performance or grip strength were more likely to be observed at the 10-year follow-up.

The current analysis did not examine the order in which physical and cognitive declines occurred. One study found that midlife changes in fluid cognition predicted levels of physical performance 10 years after the onset of cognitive decline (Buracchio, Dodge, Howieson, Wasserman, & Kave, 2010), whereas Kuh and colleagues (2009) found that gait speed declined more than a decade before the onset of cognitive impairment. This suggests that the complex relationships between physical performance and cognition are differentially susceptible to change and may depend on an individual's age. Future analyses should determine the order in which declines occur as well as identify patterns and rates of change in cognitive and functional decline.

Results from the current study highlight the complex relationship between BMI, physical performance, and cognition in older adults. Although higher BMI at baseline is associated with better grip strength at baseline, it is also associated with accelerated declines in grip strength over 10 years. These accelerated declines in grip strength negatively affect memory and reasoning performance. Better grip strength and cognitive performance at baseline are also associated with slower declines in cognition over a 10-year period.

Chapter 5. Discussion and Public Health Implications

The current study examined the dynamic relationship between body weight (defined by BMI), physical performance (defined using handgrip strength), and cognition in a sample of older adults participants in the ACTIVE trial over a 10-year period. Excess weight affects virtually every aspect of an individual's health and is linked with a variety of negative health outcomes including diabetes, heart disease, impaired respiratory and cognitive function, arthritis, and an increased risk of death. Body weight is one potential modifiable risk factor for both cognitive and functional impairments but the relationship between body weight and cognitive and functional abilities is complex and inconclusive.

Findings from the current proposal highlight the complex relationship between physical performance and cognitive performance in older adults. Results from the current analyses suggest that higher BMI at baseline was associated with both cognitive and functional performance. Results from Aim 1 suggest that better performance on memory, reasoning, speed, and Digit Symbol tasks was associated with attenuated declines in BMI over a 10-year period. Furthermore, changes in cognition were associated with changes in BMI, suggesting that slower cognitive declines were associated with a greater increase in BMI.

Aim 2 explored the mediated effect of grip-strength on weight-related changes in BMI. Findings revealed that a higher BMI at baseline was associated with better handgrip strength at baseline and accelerated declines on grip strength over time; whereas higher grip strength at baseline was associated with slower declines in cognition over time. Slower declines in grip strength were associated with slower declines in memory and reasoning, but not slower declines in speed or the Digit Symbol Task. There was an

indirect effect of BMI on cognition through changes in grip strength in the memory and reasoning outcomes, such that, a higher BMI was associated with accelerated declines in grip strength, which in turn were associated with accelerated declines in cognition. Results in the speed group were marginally significant ($p=.08$). These findings are provocative given the large body of research in older adults suggesting that excess weight is protective against cognitive declines.

Strengths

This proposal has several strengths and limitations. The ACTIVE study allows for the observation of cognitively healthy older adults without severe functional limitations at baseline as they transitioned into an age with the highest risk of cognitive impairment. In addition, the randomized longitudinal design allowed for changes in obesity, physical functioning, and cognitive functioning to be explored while ruling out potential baseline differences among individuals. Each targeted domain of cognition (i.e., memory, reasoning, and processing speed) was measured using multiple, validated cognitive tests. Stringent protocols were used to ensure testing environments were equivalent across the six sites, in addition to careful quality control measures. Furthermore, recruitment strategies ensured that a diverse sample of older adults was included in the ACTIVE study. Recruitment occurred in six geographically distinct regions in the United States and resulted in a sample of individuals with diverse demographic and socioeconomic backgrounds.

Limitations

Because this is a longitudinal study of older adults at least 65 years of age at baseline (M=74.5 years) with 10 years of follow-up, attrition was an issue. At the 10th annual follow-up, only 43.5% of the original sample (1220/2802) were assessed. Of the 1,578 participants who were deactivated or lost to follow-up, death was the primary reason for non-participation (Table 3). Although rates of attrition appear large, the rates are comparable to other longitudinal studies of older adults (Chatfield, Brayne, & Matthews, 2005).

Table 3. Reasons for deactivation across 10 years of follow-up

| Reason for deactivation | N | % |
|--------------------------------|----------|----------|
| Death | 634 | 40.2 |
| Subject decision | 555 | 35.2 |
| Site decision | 276 | 17.5 |
| Family refused access | 52 | 3.3 |
| Lost to follow-up | 61 | 3.9 |

Participants who at baseline, were younger, female, married, had fewer physical and mental health problems, and better grip strength were more likely to participate in the 10-year follow-up (Table 4). Individuals with better cognitive performance were also more likely to be retained at the 10th annual follow-up. Participation in the 10-year follow-up was *not* associated with baseline BMI.

Table 4. Baseline characteristics of participants by 10th annual status

| | Not retained (n=1582) | Retained (n=1220) | <i>p</i> -value |
|----------------|--------------------------|----------------------|-----------------|
| Age, mean (SD) | 75.0 (6.2) | 71.8 (4.9) | <.0001 |
| Sex, n (%) | | | <.0001 |
| Male | 430 (27) | 246 (20) | |
| Female | 1152 (73) | 974 (80) | |
| Race, n (%) | | | .04 |

| | | | |
|---------------------------------------|-------------|-------------|--------|
| White | 1130 (71) | 924 (76) | |
| African American | 440 (29) | 288 (24) | |
| Education, n (%) | | | .05 |
| No college | 1166 (74) | 857 (70) | |
| College (≥ 16 years) | 416 (26) | 361 (30) | |
| Marital status, n (%) | | | <.0001 |
| Not married | 1062 (67) | 731 (60) | |
| Married | 519 (33) | 488 (40) | |
| Depressive symptoms, mean (SD) | 5.8 (5.4) | 4.5 (4.7) | <.0001 |
| SF-36 Physical Functioning, mean (SD) | 64.2 (24.8) | 74.7 (21.8) | <.0001 |
| Health conditions, n (%) | 2.4 (1.5) | 2.0 (1.4) | <.0001 |
| Grip strength, mean (SD) | 24.69 (8.3) | 25.66 (8.6) | <.01 |
| Body mass index, n (%) | | | .11 |
| Normal weight (BMI 18.5-24.9) | 430 (28) | 292 (24) | |
| Overweight (BMI 25-29.9) | 612 (39) | 486 (40) | |
| Class I obesity (BMI 30-34.9) | 308 (19) | 275 (22) | |
| Class II obesity (\geq BMI 35) | 198 (12) | 155 (12) | |
| Diabetes, n (%) | | | <.001 |
| Yes | 234 (15) | 124 (10) | |
| No | 1346 (85) | 1095 (90) | |
| Myocardial infarction, n (%) | | | <.0001 |
| Yes | 223 (14) | 86 (7) | |
| No | 1348 (86) | 1129 (93) | |
| Hypertension, n (%) | | | <.001 |
| Yes | 854 (54) | 574 (47) | |
| No | 717 (46) | 639 (53) | |
| High cholesterol, n (%) | | | .17 |
| Yes | 675 (43) | 551 (46) | |
| No | 879 (57) | 645 (54) | |
| Stroke, n (%) | | | .07 |
| Yes | 122 (8) | 73 (6) | |
| No | 1448 (92) | 1139 (94) | |
| Cognitive performance, mean (SD) | | | |
| Mini-Mental State Exam score | 27.0 (2.0) | 27.7 (1.9) | <.0001 |
| Memory composite | -0.6 (2.4) | 0.9 (2.4) | <.0001 |
| Reasoning composite | -0.6 (2.5) | 0.8 (2.6) | <.0001 |
| Processing speed composite | 0.5 (2.4) | -0.7 (2.4) | <.0001 |
| Everyday function composite | 0.2 (2.1) | -0.3 (1.9) | <.0001 |

A second limitation is the nature of the ACTIVE sample. The cohort is volunteer-based and at the time of recruitment, was comprised of a relatively healthy sample of older adults (due in large part to the stringent exclusion criteria previously discussed).

Because of this, ACTIVE participants likely represent a more resilient group of older adults compared to the general population. In fact, this is evident in the lack of functional declines seen in the control group at the 24-month follow-up (Wolinsky et al., 2006). Generalizability may therefore be limited. Other primary limitations include self-report measures of medical disorders and a single measure of adiposity.

Public Health Significance

Globally, a new case of dementia is diagnosed every seven seconds (Ferri et al., 2005) and represents a significant public health challenge. Modifiable factors associated with cognitive functioning represent a promising area in public health. Analyses in the current proposal explored how obesity and physical functioning affect cognition in older adults. Findings clarify the extent to which weight in older adults is associated with changes in functional and cognitive performance. From a public health perspective, the question remains how to best identify older adults at risk for future cognitive and functional declines.

The most recent meta-analysis of midlife obesity and dementia calculated the population attributable risk (PAR), defined as the percentage of individuals suffering from dementia attributable to the risk factor of midlife obesity, using a sample of over 50,000 individuals (Loef & Walach, 2013). Unlike results reported by Anstey and colleagues (2011), Loef and Walach (2013) found no association between underweight BMI and AD risk. The adjusted PARs were calculated for both men and women in 2010, 2030, and 2050. Between 2010 and 2030, an additional 7.8% of dementia cases in men and 5.9% of dementia cases in women would be attributable to midlife obesity; whereas between 2010 and 2050 an additional 10.7% of dementia cases in men and 8.5%

dementia cases in women would be attributable to midlife obesity (Loef & Walach, 2013). Along with the currently increasing rates of obesity in midlife, Loef and Walach's (2013) findings suggest that the effects of obesity on dementia risk will be felt for many decades to come.

The protective mechanisms by which some obese individuals avoid the detrimental consequences of obesity are not well understood. It is still unclear if obesity per se or rather the increased risk of chronic health conditions (e.g., Type II diabetes, coronary heart disease, or hypertension) is associated with negative health outcomes. One possible explanation for the differential effects of obesity may be related to fat distribution. Several studies have shown that increased visceral and abdominal fat are associated with negative health outcomes, independent of overall adiposity (Fox et al., 2007; Janssen, Katzmarzyk, & Ross, 2004; Koster et al., 2010).

The current analyses used body mass index (BMI) as a measure of adiposity in older adults. However, some findings suggest that waist circumference (WC) and waist-to-hip ratio (WHR) have a stronger relationship with cognitive performance and dementia risk when compared with BMI. WC and WHR measure central obesity and reflect the abdominal distribution of body fat whereas BMI is a measure of overall adiposity. Central obesity is a stronger risk factor for cardiovascular disease and mortality compared with BMI (Whitmer et al., 2008). Visceral, or abdominal, fat is more metabolically active than subcutaneous fat and has a stronger link to insulin resistance (Elias, Goodell, & Waldstein, 2012).

As age increases, the association between cardiovascular risk factors (i.e., hypertension, hypercholesterolemia, and obesity) and cognitive functioning attenuates.

This diminished risk may be attributable to attrition due to morbidity and mortality of individuals with poor health in midlife who are also likely to perform worse on tests of cognitive functioning compared to those with better health (Elias, Goodell, & Waldstein, 2012). Future research is still needed to elucidate the mechanisms by which obesity influences both cognitive functioning and dementia risk in later life.

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Table 5. Baseline characteristics of participants by body mass index categories

| | Body Mass Index Categories (N=2,788) | | | | | p value | |
|---------------------------|--------------------------------------|-----------------------------|----------------------------|------------------|-----------------------------|--------------|-----------------------------|
| | Underweight (n=77) | Normal weight (n=677) | Over weight (n=1098) | Obese (n=583) | Class I obese (n=353) | | Class II obese (n=11) |
| Age, M(SD) | 74.7 (6.6) | 74.9 (6.4) | 73.9 (5.9) | 72.8 (5.3) | 71.2 (4.9) | 71.2 (4.4) | <.0001 |
| Women, n (%) | 67 (87.0) | 499 (73.7) | 774 (70.5) | 466 (79.9) | 209 (59.2) | 100 (90.9) | <.0001 |
| Race, n (%) | | | | | | | <.0001 |
| White | 59 (76.6) | 568 (83.8) | 803 (73.1) | 403 (69.1) | 156 (44.1) | 59 (53.6) | <.0001 |
| Years of education, M(SD) | 13.8 (2.7) | 14.1 (2.8) | 13.6 (2.7) | 13.1 (2.6) | 12.9 (2.6) | 12.5 (2.4) | <.0001 |
| Hypertension groups, n(%) | | | | | | | <.0001 |
| Normotensive | 20 (26.3) | 214 (32.2) | 197 (18.4) | 77 (13.6) | 27 (11.7) | 10 (9.9) | |
| Prehypertension | 27 (35.5) | 246 (37.0) | 421 (39.4) | 194 (32.2) | 74 (32.0) | 31 (30.7) | |
| Stage 1 hypertension | 19 (23.7) | 144 (21.7) | 318 (29.7) | 186 (32.8) | 79 (34.2) | 40 (39.6) | |
| Stage 2 hypertension | 11 (14.4) | 60 (9.0) | 133 (12.4) | 110 (19.4) | 51 (22.1) | 20 (19.8) | |
| Diabetes, n (%) | 3 (0.8) | 44 (12.4) | 124 (34.9) | 87 (24.5) | 64 (18.0) | 33 (9.3) | <.0001 |
| Cognitive function, M(SD) | | | | | | | |
| MMSE score | 27.6 (1.8) | 27.3 (1.9) | 27.3 (2.0) | 27.4 (1.9) | 27.3 (2.1) | 26.4 (2.2) | <.01 |
| Memory composite | 0.19 (2.4) | -0.15 (2.5) | -0.01 (2.4) | 0.03 (2.2) | 0.15 (2.2) | -0.15 (2.0) | >.05 |
| Reasoning composite | -0.17 (0.9) | 0.02 (0.9) | 0.01 (0.9) | -0.03 (0.8) | 0.03 (0.9) | -0.17 (0.9) | >.05 |
| Speed composite | 0.16 (0.8) | 0.09 (0.8) | -0.03 (0.8) | -0.02 (0.8) | -0.10 (0.8) | -0.001 (0.8) | <.01 |
| Digit Symbol Substitution | 91.6 (6.1) | 91.8 (2.7) | 91.7 (3.1) | 91.8 (3.1) | 91.7 (4.3) | 91.5 (3.1) | >.05 |

Body mass index was categorized according to the following: Underweight, <20 kg/m²; normal weight, 20-24.9 kg/m²; overweight 25-29.9 kg/m²; obese 30-34.9 kg/m²; class I obese 35-39.9 kg/m²; class II obese ≥ 40 kg/m²; Hypertension categorized as: Normal – SBP <120mmHg and DBP <80mmHg; Prehypertension-SBP 120-139mmHg or DBP 80-89mmHg; Stage 1 hypertension-SBP 140-159mmHg or DBP 90-99mmHg; stage 2 hypertension – SBP ≥160mmHg or DBP ≥100mmHg

Table 6. Parallel process growth model – unadjusted results

| Standardized Results† | Memory | | Reasoning | | Speed | | DSSST | |
|--------------------------------------|------------------|----|------------------|----|------------------|----|------------------|----|
| | Coefficient (SE) | SE | Coefficient (SE) | SE | Coefficient (SE) | SE | Coefficient (SE) | SE |
| Residual Correlations | | | | | | | | |
| Intercept with intercept | 0.02 (0.02) | | -0.01 (0.02) | | -0.08 (0.02) | ** | 0.0002 (0.02) | ** |
| Slope with slope | 0.29 (0.06) | ** | 0.28 (0.05) | ** | -0.28 (0.07) | ** | 0.25 (0.05) | ** |
| Regressions | | | | | | | | |
| BMI slope on | | | | | | | | |
| BMI intercept | -0.21 (0.04) | ** | -0.21 (0.04) | ** | -0.22 (0.04) | ** | -0.21 (0.04) | ** |
| Cognition intercept | 0.05 (0.04) | | 0.07 (0.03) | * | -0.15 (0.04) | ** | 0.08 (0.04) | * |
| Cognition slope on | | | | | | | | |
| BMI intercept | 0.02 (0.04) | | 0.09 (0.04) | * | 0.02 (0.05) | | -0.01 (0.04) | |
| Cognition intercept | -0.08 (0.06) | | -0.004 (0.04) | | -0.20 (0.05) | ** | 0.02 (0.04) | |
| Intervention group | -0.09 (0.05) | | -0.19 (0.04) | ** | 0.57 (0.05) | ** | -0.07 (0.04) | * |
| Re-test effect on intervention group | 0.32 (0.04) | ** | 0.65 (0.04) | ** | -0.80 (0.02) | ** | 0.08 (0.04) | * |
| Model Fit Statistics | | | | | | | | |
| χ^2 (df) | 288.78 (68) | | 512.25 (68) | | 530.95 (68) | | 247.70 (67) | |
| RMSEA/SRMR | 0.03/0.03 | | 0.05/0.03 | | 0.05/0.07 | | 0.03/0.03 | |
| CFI | 0.99 | | 0.98 | | 0.97 | | 0.99 | |

†Cognitive outcomes were standardized with M(50), SD(10); * p < .01 ** p < .0001

Note: Lower scores on the speed composite indicate better performance

Table 7. Parallel process growth model –adjusted results

| Standardized Results† | Memory | Reasoning | Speed†† | DSS† |
|-------------------------------------|------------------|------------------|------------------|------------------|
| | Coefficient (SE) | Coefficient (SE) | Coefficient (SE) | Coefficient (SE) |
| Residual Correlations | | | | |
| Intercept with intercept | 0.02 (0.02) | -0.01 (0.02) | -0.08 (0.02) | 0.002 (0.02) |
| Slope with slope | 0.29 (0.06)** | 0.29 (0.05)** | -0.35 (0.10)** | 0.25 (0.05)** |
| Regressions | | | | |
| BMI slope on | | | | |
| BMI intercept | -0.20 (0.04)** | -0.20 (0.04)** | -0.21 (0.04)** | -0.20 (0.04)** |
| Cognition intercept | 0.07 (0.04)* | 0.08 (0.03)* | -0.16 (0.04)** | 0.09 (0.04)* |
| Cognition slope on | | | | |
| BMI intercept | 0.03 (0.04) | 0.10 (0.04)* | 0.02 (0.05) | 0.01 (0.04) |
| Cognition intercept | -0.02 (0.06) | 0.02 (0.04) | -0.14 (0.06)* | 0.06 (0.04) |
| Intervention group | -0.04 (0.04) | -0.14 (0.04)** | 0.62 (0.07)** | -0.02 (0.04) |
| Retest effect on intervention group | 0.32 (0.05)** | 0.64 (0.04)** | -0.82 (0.02)** | 0.05 (0.04) |
| Age on | | | | |
| BMI intercept | -0.21 (0.02)** | -0.21 (0.02)** | -0.19 (0.02)** | -0.22 (0.02)** |
| Cognition intercept | -0.39 (0.02)** | -0.32 (0.02)** | 0.50 (0.02)** | -0.30 (0.02)** |
| BMI slope | -0.10 (0.03)* | -0.13 (0.04)** | -0.15 (0.03)** | -0.13 (0.03)** |
| Cognition slope | -0.30 (0.04)** | -0.23 (0.05)** | -0.01 (0.03) | -0.25 (0.04)** |
| Sex on | | | | |
| BMI intercept | -0.08 (0.02)** | -0.07 (0.02)** | -0.09 (0.02)** | -0.07 (0.02)** |
| Cognition intercept | -0.14 (0.02)** | 0.06 (0.02)* | -0.06 (0.03)* | -0.09 (0.02)** |
| BMI slope | 0.03 (0.03) | 0.03 (0.03) | 0.01 (0.03) | -0.04 (0.03) |
| Cognition slope | 0.04 (0.05) | -0.04 (0.05) | -0.03 (0.03) | -0.05 (0.04) |
| Race on | | | | |
| BMI intercept | -0.15 (0.02)** | -0.15 (0.02)** | -0.16 (0.02)** | -0.15 (0.02)** |
| Cognition intercept | 0.21 (0.02)** | 0.31 (0.02)** | -0.10 (0.02)** | 0.26 (0.02)** |
| BMI slope | 0.01 (0.04) | -0.02 (0.04) | -0.02 (0.04) | 0.01 (0.04) |
| Cognition slope | -0.13 (0.05)** | -0.03 (0.04) | 0.02 (0.03) | -0.13 (0.04)** |

| | | | | | |
|----------------------|----------------|----------------|----------------|----------------|----------------|
| Diabetes on | | | | | |
| BMI intercept | 0.21 (0.02)** | 0.22 (0.02)** | 0.21 (0.02)** | 0.21 (0.02)** | 0.21 (0.02)** |
| Cognition intercept | -0.07 (0.02)** | -0.06 (0.02)* | 0.08 (0.02)** | -0.10 (0.02)** | -0.10 (0.02)** |
| BMI slope | 0.02 (0.04) | 0.02 (0.04) | 0.01 (0.04) | 0.04 (0.04) | 0.04 (0.04) |
| Cognition slope | -0.05 (0.05) | -0.06 (0.04) | -0.01 (0.03) | -0.11 (0.04)* | -0.11 (0.04)* |
| Hypertension on | | | | | |
| BMI intercept | 0.18 (0.02)** | 0.18 (0.02)** | 0.18 (0.02)** | 0.14 (0.02)** | 0.14 (0.02)** |
| Cognition intercept | -0.05 (0.02)* | -0.08 (0.02)** | 0.05 (0.02)* | -0.06 (0.02)* | -0.06 (0.02)* |
| BMI slope | -0.08 (0.04)* | -0.07 (0.03)* | -0.08 (0.03)* | -0.10 (0.04)* | -0.10 (0.04)* |
| Cognition slope | 0.03 (0.05) | -0.01 (0.04) | -0.01 (0.03) | 0.06 (0.05) | 0.06 (0.05) |
| Education on | | | | | |
| BMI intercept | -0.16 (0.02)** | -0.13 (0.02)** | -0.17 (0.02)** | -0.15 (0.02)** | -0.15 (0.02)** |
| Cognition intercept | 0.31 (0.02)** | 0.43 (0.02)** | -0.20 (0.02)** | 0.28 (0.02)** | 0.28 (0.02)** |
| BMI slope | -0.01 (0.03) | 0.03 (0.03) | 0.01 (0.03) | 0.01 (0.03) | 0.01 (0.03) |
| Cognition slope | 0.06 (0.04) | -0.11 (0.04)* | 0.02 (0.03) | 0.002 (0.04) | 0.002 (0.04) |
| MMSE score on | | | | | |
| BMI intercept | -0.07 (0.02)** | -0.05 (0.02)* | -0.09 (0.02)** | -0.06 (0.02)** | -0.06 (0.02)** |
| Cognition intercept | 0.52 (0.01)** | 0.52 (0.01)** | -0.36 (0.02)** | 0.40 (0.02)** | 0.40 (0.02)** |
| BMI slope | -0.001 (0.03) | -0.001 (0.03) | -0.001 (0.04) | 0.01 (0.03) | 0.01 (0.03) |
| Cognition slope | 0.01 (0.04) | 0.01 (0.02) | 0.03 (0.03) | -0.01 (0.04) | -0.01 (0.04) |
| Model Fit Statistics | | | | | |
| χ^2 (df) | 399.89 (120) | 668.31 (120) | 693.77 (120) | 362.08 (119) | 362.08 (119) |
| RMSEA/SRMR | 0.03/0.02 | 0.04/0.02 | 0.04/0.04 | 0.03/0.03 | 0.03/0.03 |
| CFI | 0.99 | 0.98 | 0.97 | 0.99 | 0.99 |

†Cognitive outcomes were standardized with M(50), SD(10); *p < .01 **p < .0001; Sex (0=female; 1=male); Race (0=Black; 1=White) ††Lower scores on the speed composite indicate better performance

Table 8. Baseline characteristics of participants by sex-specific grip strength tertiles

| | Grip Strength – tertiles by sex (N=2,788) | | | | | | | |
|----------------------------|---|---------------------|--------------------|------------|-------------------|---------------------|--------------------|------------|
| | Women | | | Men | | | | |
| | First (2-19kg) | Second (20-24kg) | Third (25-50kg) | p value | First (9-30kg) | Second (31-38kg) | Third (39-64kg) | p value |
| Age, M (SD) | 75.2 (6.2) | 73.6 (5.5) | 71.4 (5.0) | <.0001 | 76.4 (6.6) | 73.1 (5.5) | 71.4 (4.5) | <.0001 |
| White, n (%) | 455 (85.5) | 517 (73.0) | 334 (58.5) | <.0001 | 173 (83.2) | 178 (82.0) | 136 (78.6) | N.S. |
| Years of education, M (SD) | 13.4 (2.5) | 13.1 (2.4) | 13.3 (2.7) | N.S. | 13.9 (3.0) | 14.7 (2.7) | 14.5 (3.1) | .04 |
| Hypertension groups, n (%) | | | | | | | | |
| Normotensive | 118 (23.1) | 130 (18.9) | 112 (20.1) | N.S. | 39 (19.0) | 47 (21.9) | 28 (16.1) | N.S. |
| Prehypertension | 179 (35.1) | 254 (36.9) | 197 (35.4) | | 73 (35.6) | 88 (41.1) | 63 (36.4) | |
| Stage 1 hypertension | 153 (30.0) | 186 (27.0) | 156 (28.0) | | 65 (31.7) | 60 (28.0) | 57 (32.9) | |
| Stage 2 hypertension | 59 (11.6) | 117 (17.0) | 91 (16.3) | | 28 (13.6) | 19 (8.8) | 25 (14.4) | |
| Diabetes, n (%) | 69 (12.9) | 89 (12.5) | 69 (12.1) | N.S. | 34 (16.3) | 24 (11.0) | 18 (10.4) | N.S. |
| Osteoporosis, n (%) | 153 (29.0) | 159 (22.6) | 84 (14.8) | <.0001 | 4 (1.9) | 6 (2.7) | 2 (1.1) | N.S. |
| Body Mass Index, n (%) | | | | | | | | |
| Underweight (<20) | 28 (5.2) | 21 (2.9) | 8 (1.4) | <.0001 | 6 (2.9) | 2 (0.9) | 1 (0.5) | .02 |
| Normal (20-24.9) | 171 (32.2) | 163 (23.0) | 103 (18.1) | | 68 (32.8) | 51 (23.5) | 32 (18.5) | |
| Overweight (25-29.0) | 180 (33.9) | 266 (37.6) | 208 (36.6) | | 90 (43.4) | 101 (46.5) | 96 (55.4) | |
| Obese (30-34.9) | 97 (18.3) | 153 (21.6) | 149 (26.2) | | 32 (15.4) | 49 (22.5) | 29 (16.7) | |
| Class I obese (35-39.9) | 36 (6.7) | 67 (9.4) | 69 (12.1) | | 9 (4.3) | 10 (4.6) | 13 (7.5) | |
| Class II obese (>40) | 18 (3.4) | 36 (5.1) | 31 (5.5) | | 2 (0.9) | 4 (1.8) | 2 (1.1) | |
| Cognitive function, M (SD) | | | | | | | | |
| MMSE score | 27.3 (2.1) | 27.3 (2.0) | 27.3 (1.9) | N.S. | 27.2 (2.0) | 27.7 (2.7) | 27.7 (2.0) | .02 |
| Memory composite | 0.02 (2.4) | 0.25 (2.3) | 0.27 (2.2) | .07 | -1.26 (2.4) | -0.37 (2.2) | -0.09 (2.4) | <.0001 |
| Reasoning composite | -0.08 (0.9) | 0.01 (0.8) | 0.03 (0.08) | .04 | -0.14 (0.9) | 0.20 (0.9) | 0.26 (0.9) | <.0001 |
| Speed composite | 0.19 (0.7) | -0.03 (0.8) | -0.16 (0.8) | <.0001 | 0.29 (0.7) | -0.13 (0.8) | -0.42 (0.9) | <.0001 |

Body mass index was categorized according to the following: Underweight, <20 kg/m²; normal weight, 20-24.9 kg/m²; overweight 25-29.9 kg/m²; obese 30-34.9kg/m²; class I obese 35-39.9 kg/m²; class II obese ≥ 40kg/m²; Hypertension categorized as: Normal – SBP <120mmHg and DBP <80mmHg; Prehypertension-SBP 120-139mmHg or DBP 80-89mmHg; Stage I hypertension- SBP 140-159mmHg or DBP 90-99mmHg; stage 2 hypertension – SBP ≥160mmHg or DBP ≥100mmHg

Table 9. Covariate effects on longitudinal mediation of grip strength on weight-related changes in cognition

| | Memory Estimate | Reasoning Estimate | Speed [†] Estimate | DSST Estimate |
|-----------------------|----------------------|-----------------------|--------------------------------|----------------------|
| Age on | | | | |
| GS intercept | -0.23 ^{***} | -0.23 ^{***} | -0.23 ^{***} | -0.23 ^{***} |
| Cognition intercept | -0.35 ^{***} | -0.30 ^{***} | 0.51 ^{***} | -0.01 |
| GS slope | -0.18 ^{***} | -0.17 ^{***} | -0.18 ^{***} | -0.19 ^{***} |
| Cognition slope | -0.38 ^{***} | -0.25 ^{***} | 0.25 ^{***} | -0.02 |
| Sex on | | | | |
| GS intercept | 0.70 ^{***} | 0.70 ^{***} | 0.70 ^{***} | 0.70 ^{***} |
| Cognition intercept | -0.21 ^{***} | -0.04 ^{**} | -0.01 | -0.05 |
| GS slope | 0.38 ^{***} | 0.37 ^{***} | 0.37 ^{**} | 0.36 ^{***} |
| Cognition slope | -0.18 ^{**} | -0.34 | 0.11 | -0.18 [*] |
| Race on | | | | |
| GS intercept | -0.20 ^{***} | -0.20 ^{***} | -0.20 ^{***} | -0.20 ^{***} |
| Cognition intercept | 0.21 ^{***} | 0.26 ^{***} | -0.12 ^{***} | 0.18 [*] |
| GS slope | -0.02 | -0.03 | -0.004 | -0.03 |
| Cognition slope | 0.04 | 0.06 | -0.06 | -0.23 ^{**} |
| Years of education on | | | | |
| GS intercept | 0.02 | 0.02 | 0.02 | 0.02 |
| Cognition intercept | 0.20 ^{***} | 0.31 ^{***} | -0.09 ^{***} | 0.06 |
| GS slope | 0.01 | -0.01 | 0.02 | 0.02 |
| Cognition slope | 0.09 [*] | -0.10 [*] | -0.04 | 0.06 |
| MMSE on | | | | |
| GS intercept | 0.03 [*] | 0.03 [*] | 0.03 [*] | 0.03 [*] |
| Cognition intercept | 0.37 ^{***} | 0.33 ^{***} | -0.21 ^{***} | 0.20 ^{**} |
| GS slope | -0.01 | -0.02 | 0.00 | -0.03 |
| Cognition slope | 0.01 | 0.01 | -0.14 ^{**} | -0.03 |
| Diabetes on | | | | |
| GS intercept | -0.07 ^{***} | -0.07 ^{***} | -0.07 ^{***} | -0.07 ^{***} |
| Cognition intercept | -0.04 ^{**} | -0.01 | 0.08 ^{***} | -0.03 |
| GS slope | -0.02 | -0.02 | -0.02 | -0.02 |
| Cognition slope | -0.08 [*] | -0.07 | 0.02 | -0.05 |
| Hypertension on | | | | |
| GS intercept | -0.02 | -0.02 | -0.02 | -0.02 |
| Cognition intercept | 0.02 | -0.01 | 0.004 | 0.09 |
| GS slope | -0.04 | -0.04 | -0.04 | -0.06 |
| Cognition slope | 0.02 | -0.01 | 0.04 | -0.08 |
| χ^2 (df) | 623.2 (131) | 968.4 (131) | 952.9 (131) | 593.7 (121) |
| RMSEA/SRMR | 0.04/0.03 | 0.05/0.04 | 0.05/0.05 | 0.03/0.05 |
| CFI | 0.98 | 0.97 | 0.95 | 0.95 |

[†]Note: Lower scores on the speed composite represent better performance

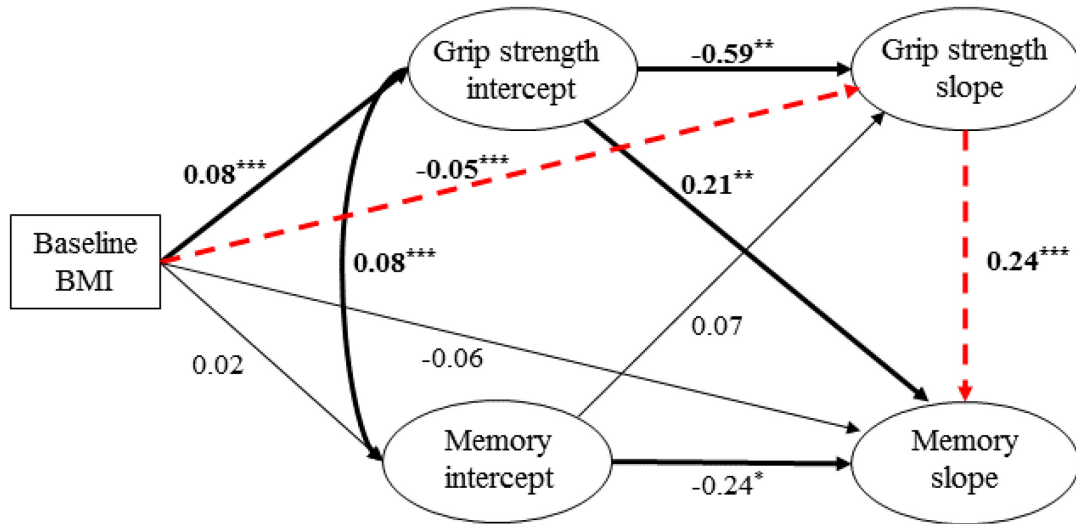
***p<.0001; **p<.01, *p<.05

Table 10. Bootstrapped estimates of cognition mediated by grip strength

| | Memory | Reasoning | Speed* | DSSST |
|--|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| | Estimate (95% CI) | Estimate (95% CI) | Estimate (95% CI) | Estimate (95% CI) |
| BMI effect on | | | | |
| Grip Strength (GS) intercept | 0.08 (0.05, 0.11) p<.0001 | 0.08 (0.05, 0.11) p<.0001 | 0.08 (0.05, 0.11) p<.0001 | 0.08 (0.05, 0.11) p<.0001 |
| GS slope | -0.05 (-0.07, -0.03) p<.0001 | -0.05 (-0.07, -0.03) p<.0001 | -0.05 (-0.07, -0.03) p<.0001 | -0.05 (-0.07, -0.03) p<.0001 |
| BMI effect on cognition slope via GS slope | -0.01 (-0.02, -0.004) p<.001 | -0.01 (-0.02, -0.002) p=.01 | 0.01 (-0.001, 0.01) | 0.004 (-0.01, 0.01) |
| BMI effect on cognition slope via GS intercept | 0.02 (0.004, 0.03) p=.01 | 0.03 (0.01, 0.05) p<.0001 | -0.02 (-0.03, -0.002) p=.02 | 0.02 (-0.001, 0.03) |
| Direct effect from GS slope to cognition slope | 0.24 (0.12, 0.36) p<.0001 | 0.18 (0.06, 0.29) p=.003 | -0.14 (-0.29, 0.01) p=.06 | -0.09 (-0.29, 0.11) |
| Direct effect from GS intercept to cognition slope | 0.21 (0.07, 0.35) p<.01 | 0.36 (0.23, 0.47) p<.0001 | -0.21 (-0.36, -0.05) p<.01 | 0.21 (0.01, 0.42) p<.05 |
| Model fit statistics | | | | |
| χ^2 (df) | 623.2 (131) | 968.4 (131) | 952.9 (131) | 593.7 (121) |
| RMSEA/SRMR | 0.04/0.03 | 0.05/0.04 | 0.05/0.05 | 0.03/0.05 |
| CFI | 0.98 | 0.97 | 0.95 | 0.95 |

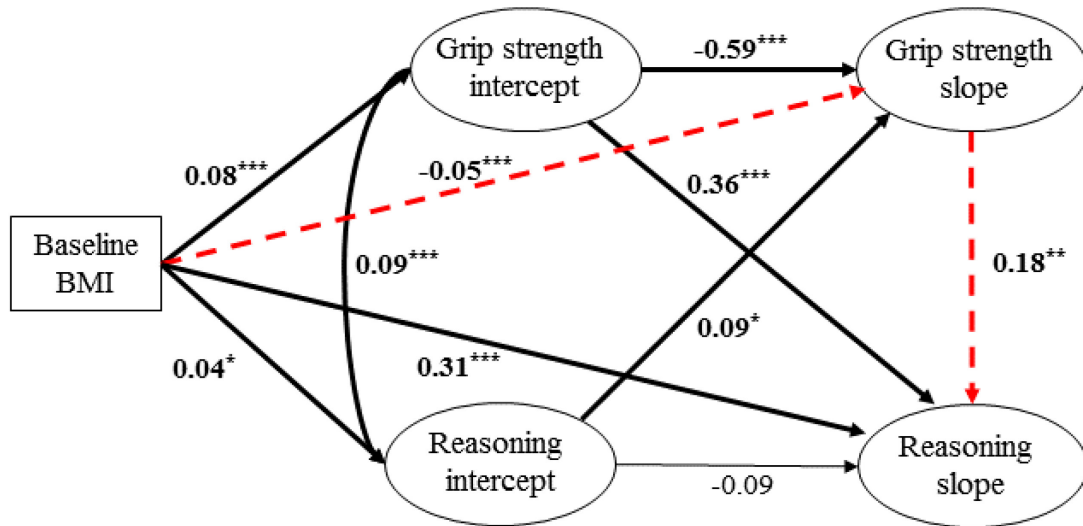
*Note: Lower scores on the speed composite represent better performance

Figure 4. Parallel process latent growth model for the mediating effect of grip strength on memory



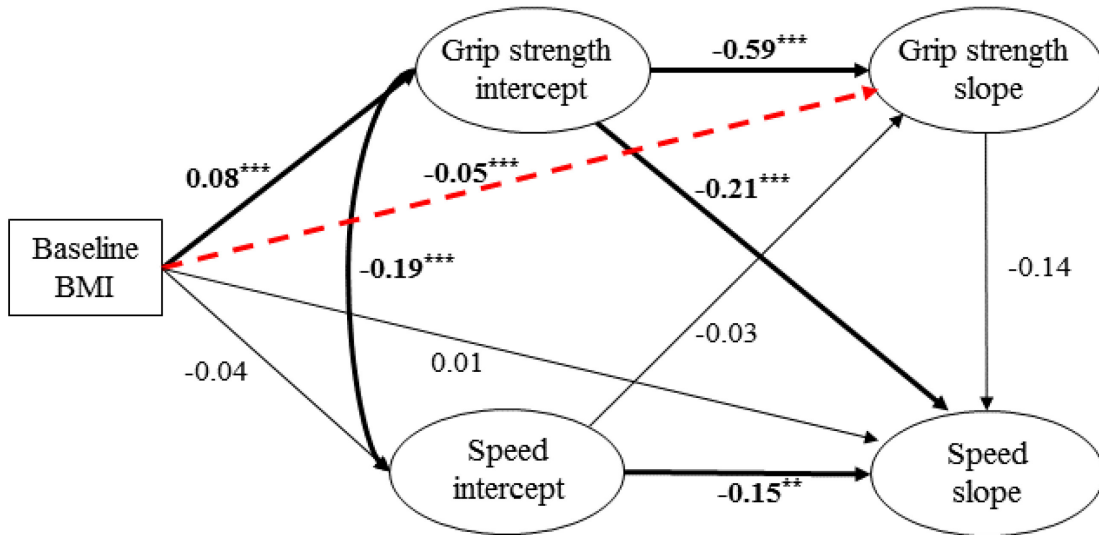
Legend. Mediation model with handgrip strength as a mediator of the relationship between BMI at baseline and memory performance. Observed variables, error terms, and structural paths from covariates to each growth curve factor were omitted from this figure for presentation purposes. Dashed red arrows represent the statistically significant mediating pathways. * $p < .05$; ** $p < .01$; *** $p < .0001$

Figure 5. Parallel process latent growth model for the mediating effect of grip strength on reasoning



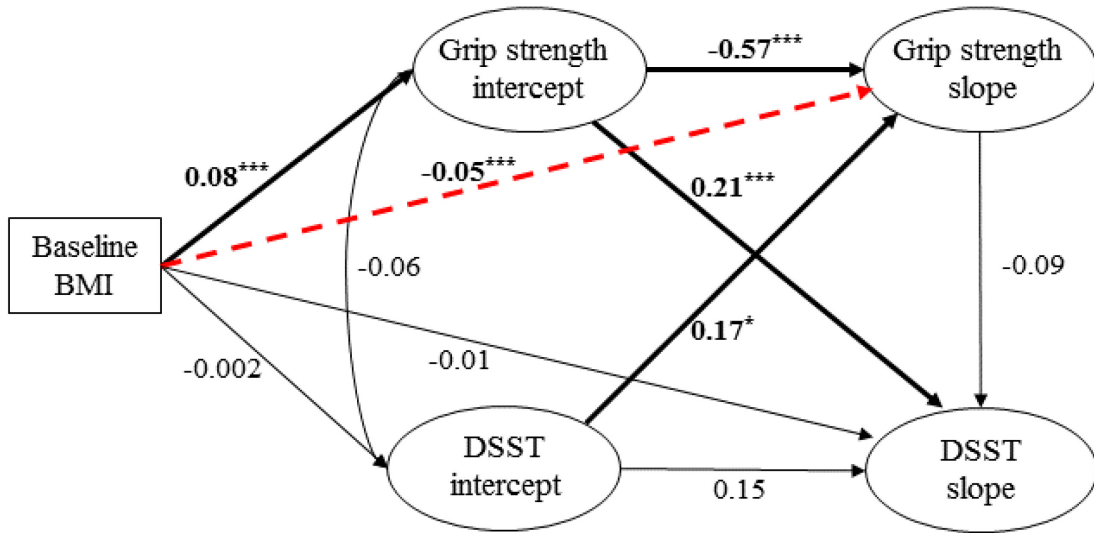
Legend. Mediation model with handgrip strength as a mediator of the relationship between BMI at baseline and reasoning performance. Observed variables, error terms, and structural paths from covariates to each growth curve factor were omitted from this figure for presentation purposes. Dashed red arrows represent the statistically significant mediating pathways. * $p < .05$; ** $p < .01$; *** $p < .0001$

Figure 6. Parallel process latent growth model for the mediating effect of grip strength on speed



Legend. Mediation model with handgrip strength as a mediator of the relationship between BMI at baseline and processing speed performance. Observed variables, error terms, and structural paths from covariates to each growth curve factor were omitted from this figure for presentation purposes. Dashed red arrows represent the statistically significant mediating pathways. * $p < .05$; ** $p < .01$; *** $p < .0001$

Figure 7. Parallel process latent growth model for the mediating effect of grip strength on digit symbol



Legend. Mediation model with handgrip strength as a mediator of the relationship between BMI at baseline and Digit Symbol Substitution Task (DSST) performance. Observed variables, error terms, and structural paths from covariates to each growth curve factor were omitted from this figure for presentation purposes. Dashed red arrows represent the statistically significant mediating pathways. * $p < .05$; ** $p < .01$; *** $p < .0001$

Curriculum Vitae

Alexandra M. Kueider

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EDUCATION

Ph.D. Mental Health, Johns Hopkins Bloomberg School of Public Health
Dissertation topic: Obesity and physical functioning: Associations with cognition in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) cohort
Advisor: Dr. George W. Rebok

M.S. Clinical Psychology, Loyola University, May 2010

B.A. Psychology, University of North Carolina – Greensboro, December 2006

RESEARCH INTERESTS

Alzheimer's disease risk factors, Cognitive aging, Epidemiology, Obesity

PUBLICATIONS

Journal Articles

Kueider AM, Parisi JM, Gross AL, & Rebok GW. (2012). Computerized cognitive training in older adults: A systematic review. *PLoS ONE* 7(7): e40588. doi: 10.1371/journal.pone.0040588

Gross AL, Parisi JM, Spira AP, **Kueider AM**, Ko JY, Saczynski JS, Samus QM, & Rebok GW (2012). Memory training interventions for older adults: a meta-analysis. *Aging and Mental Health*. doi:10.1080/13607863.2012.667783

Lohman MC, Rebok GW, Spira AP, Parisi JM, Gross AL, & **Kueider AM**. (2012). Depressive symptoms and memory performance among older adults: Results from the ACTIVE memory training intervention. *Journal of Aging and Health*.

Rebok GW, Langbaum JBS, Jones RN, Gross AL, Parisi JN, Spira AP, **Kueider A**, Petras H, & Brandt J. (2012). Memory training in the ACTIVE study: How much is needed and who benefits? *Journal of Aging and Health*.

Wennberg AM, **Kueider AM**, Spira AP, Rager R, Adams GL, & Rebok GW. (Under review). Attention Workout: Improving Cognition in Older Adults Online.

Kueider AM, Wennberg AM, Rebok GW, Parisi JM, & Spira AP. (Under review). Marital status in older adults: Associations with memory and functional abilities in the ACTIVE study.

Sullivan C, **Kueider AM**, Varvaris M, Onyike C, Gordon B, Sair H, & Schretlen DJ. (Under review). Association of perseverative errors with neural volume and integrity in adults with schizophrenia.

Vandorsall T, **Kueider AM**, Carlson M, & Schretlen DJ. (Under review). Uric acid levels and cognitive performance in older women: Results from the Women's Health and Aging Study

Journal Articles in Preparation

Kueider AM, Gross AL, Parisi JP, & Rebok GW. (In preparation). Dynamic relationship between longitudinal cognitive performance and body mass index in older adults: Results from the ACTIVE study.

- Kueider AM** & Rebok GW. (In preparation). Longitudinal mediation of grip strength on weight-related changes in cognition.
- Kueider AM**, Naeger S, & Eaton WW. (In preparation). Self-rated health and the onset of symptoms of depression in the Baltimore Epidemiologic Catchment Area Study.
- Kueider AM**, Varavis M, & Schretlen DJ. (In preparation). Association of self-imposed restrictions on driving with cognitive performance and brain volume.
- Kueider AM**, & Eaton WW. (In preparation). The association of alcohol use and depression and suicidal ideation in middle age: the Baltimore ECA study.
- Sullivan C, **Kueider AM**, Onyike C, & Schretlen DJ. (In preparation). Regression-based error analysis in the detection of behavioral variant frontotemporal dementia.

Book Chapters

- Rebok GW, Parisi JM, & **Kueider AM**. (2014). Stressors and vulnerabilities in middle and old age: Opportunities for prevention. In Z. Sloboda & H. Petra (Eds.) *Advances in Prevention Science*. Springer Science: New York.

PRESENTATIONS

- Kueider AM**. (2014). Obesity and physical functioning: Associations with cognitive in the ACTIVE study. Job talk at the National Institute on Aging Laboratory of Behavioral Neuroscience, Baltimore, MD.
- Sullivan C, **Kueider AM**, Gordon B, & Schretlen DJ. (2014). Cognitive Aging on Four Continents. Symposium at the International Neurological Society Conference, Seattle, WA.
- Schretlen DJ, **Kueider AM**, Sullivan C, & Gordon B. (2014). Cultural differences in the effects of education and illiteracy on animal naming. Symposium at the International Neurological Society Conference, Seattle, WA.

Professional Meeting Posters

- Sullivan C, **Kueider AM**, Kansal K, & Onyike C. (2014). Regression-based error analysis in a longitudinal case study of slowly progressive behavioral variant Frontotemporal Dementia (bvFTD). Poster presentation at the 9th annual International Conference on Frontotemporal Dementias, Vancouver, Canada.
- Sullivan C, **Kueider A**, Onyike C, & Schretlen D. (2014). Regression-based error analysis in behavioral variant frontotemporal dementia (bvFTD). Poster presentation at the International Neurological Society Conference, Seattle, WA.
- Kueider AM** & Rebok GW. (2014). Longitudinal mediation of grip strength of weight-related changes in cognition: Results from ACTIVE. Poster presentation at the Cognitive Aging Conference, Atlanta, GA.
- Kueider AM**, Varvaris M, & Schretlen DS. (2014). Association of self-imposed restrictions on driving with cognitive performance and brain volume. Poster presentation at the Cognitive Aging Conference, Atlanta, GA.
- Gross AL, **Kueider AM**, Sullivan C, Schretlen D. (2014). Equating five versions of the MMSE administered in 37 studies across four continents. Poster presentation at the Cognitive Aging Conference, Atlanta, GA.
- Kueider AM**, Gross AL, Parisi JP, & Rebok GW. (2013). Dynamic relationship between longitudinal cognitive performance and body mass index in older adults: Results from the ACTIVE study. Poster presentation at the Gerontological Society of America Conference, New Orleans LA.

- Wennberg AM, **Kueider AM**, Spira AP, Rager R, Adams GL, & Rebok GW. (2013). Attention Workout: Improving Cognition in Older Adults Online. Poster presentation at the Gerontological Society of America Conference, New Orleans, LA.
- Kueider AM**, Parisi JM, Gross AL, & Rebok GW. (2012). Computerized cognitive training in older adults: A systematic review. Poster presentation at Cognitive Aging Conference, Atlanta, GA.
- Gross AL, Parisi JM, Spira AP, **Kueider AM**, Ko JY, Saczynski JS, Samus QM, & Rebok GW. (2011). Does memory training work? A systematic review and meta-analysis. Poster presentation at Gerontological Society of America Conference, Boston, MA.
- Lohman MC, Rebok GW, Spira AP, Parisi JM, Gross AL, & **Kueider AM**. (2011). The effect of depression on memory and memory training intervention in older adults: Results from the Advanced Cognitive Training for Independent and Vital Elderly. Poster presentation at Gerontological Society of America Conference, Boston, MA.

TEACHING ASSISTANT

- Research Methods I (2009), Department of Psychology, Loyola University
- Research Methods II (2010), Department of Psychology, Loyola University
- Psychiatric Epidemiology (2012), Department of Mental Health, Johns Hopkins Bloomberg School of Public Health
- Psychiatric Epidemiology (2013), Department of Mental Health, Johns Hopkins Bloomberg School of Public Health

WORKSHOPS ATTENDED

- Advanced Psychometrics Methods in Cognitive Aging Research Workshop. University of California, Davis. 2014 June.
- MPLUS Workshop (Topic 3). Introductory and intermediate growth modeling. Johns Hopkins University, 2010 March.
- MPLUS Workshop (Topic 4). Advanced growth modeling, survival analysis, and missing data analysis. Johns Hopkins University, 2010 March

SERVICE

Peer Review Activities

Journal reviewer

- American Journal of Geriatric Psychiatry
- BMJ Open
- Games for Health Journal
- The Gerontologist
- Journal of Alzheimer's Disease
- Journal of Comparative Effectiveness Research
- Journals of Gerontology: Psychological Sciences
- Journal of Addiction Research and Therapy
- Psychology and Aging

Grant reviewer

- Food and Health Bureau of The Government of Hong Kong, China

PROFESSIONAL MEMBERSHIPS

- The American Public Health Association
- American Psychological Association
- Association for Psychological Science
- Gerontological Society of America

WORK EXPERIENCE

Research Assistant, Johns Hopkins Hospital

8/12-8/14

Projects

- International Neuropsychological Normative Database Initiative (INNDI) - goal of this initiative is to combine normative data from around the world for selected cognitive tests and publish these data as a free global resource. The resulting database will enable users to: (1) reference a person's test performance against that shown by healthy persons of similar age, sex, and cultural and linguistic background, (2) measure the effects of modifying test stimuli for cultural or linguistic reasons on performance, and (3) provide researchers with healthy control data
- Regression-based error analysis in the detection of behavioral variant frontotemporal dementia.
- Neurocognitive performance in Lesch-Nyhan syndrome
- Association of self-imposed driving restrictions with cognitive performance and brain volume
- Association of perseverative errors with neural volume and integrity in schizophrenia

Internship, American Institutes for Research

6/13-12/13

- Prepared issue brief "Cognitive Training: What is it and Does it Work?" for the Center on Aging
- Prepared background information for grant application using Project TALENT data to explore the association between childhood factor and healthcare expenditure in midlife

Externship, Psychometrist, Johns Hopkins Hospital

12/09-05/10

- Completed neuropsychological testing evaluations on patients referred to the Medical Psychological Clinic within the Department of Psychiatry and Behavioral Sciences at the Johns Hopkins Hospital
- Attended Medical Psychology Seminar and Neurology Grand Rounds