A WEIGHTY MATTER:

EFFECTS OF ADIPOSITY ON ADULT NEUROCOGNITIVE HEALTH

by

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ABSTRACT

There is a growing body of evidence suggesting there are modifiable vascular and metabolic risk factors for Alzheimer’s disease (AD). Despite many plausible mechanisms by which obesity could contribute, its etiological contributions remains unclear. We therefore investigated 1) the evidence linking obesity to cognitive health, 2) whether obesity in early or mid-life is associated with cognitive change and the possible factors involved, and 3) whether dietary interventions that reduce weight improve adult cognitive function. Study 1 involved a systematic literature review of the evidence linking adiposity to adult cognitive health outcomes. This revealed evidence that dementia was associated in older adults with low weight and separately with weight loss. However being overweight or obese in midlife was associated with cognitive decline and increased risk of dementia in later life. Study 2 examined the cross-sectional association between adiposity and cognitive function in a nationally representative sample of 4515 men and women, aged 20-59 years, who completed cognitive testing as part of the Third National Health and Nutrition Examination (NHANES-III). Global obesity and central obesity both predicted a small proportion of the variance on the Serial Digit Learning Task (SDLT) and the Simple Reaction Time Task (SRTT), but not the Symbol Digit Substitution Test (SDST). Frequent physical activity (PA) modified the association of SDLT and central obesity to the point that subjects who were obese or overweight but physically active showed cognitive performance similar to that of persons of normal weight. Study 3 involved a systematic literature review of the effects of weight loss interventions on adult cognitive function. The existing evidence gives mixed results, but the majority of studies reported beneficial effects of
weight loss on cognitive function, including memory. **Study 4** compared the effects of 8 weeks of intermittent fasting (IF) with the effects of standard dietary restriction for weight loss, on the cognitive function and health of 26 obese adults. IF consisted of completely fasting one day and eating *ad libitum* the next. Although no effects on cognition were apparent at 8 weeks, at 6 months post-intervention, the IF group showed improved memory, BDNF and greater loss of trunk fat. Reduced trunk fat was associated with improved memory scores. **Summary.** Results are consistent with the hypotheses that obesity is associated with cognitive deficits that can be ameliorated by weight loss and/or IF. However further research is needed.

The form and content of this abstract are approved. I recommend its publication.

Approved: Mary Coussons-Read
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<td>ADF</td>
<td>Alternate-Day Fasting</td>
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<td>BBB</td>
<td>Blood-Brain Barrier</td>
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<td>BDNF</td>
<td>Brain-Derived Neurotrophic Factor</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CR</td>
<td>Calorie Restriction</td>
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<td>CRP</td>
<td>C-Reactive Protein</td>
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<td>DR</td>
<td>Dietary Restriction</td>
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<td>GC</td>
<td>Glucocorticoid</td>
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<td>HEI</td>
<td>Healthy Eating Index</td>
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<td>HPA</td>
<td>Hypothalamic-Pituitary Adrenal</td>
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<td>KD</td>
<td>Ketogenic Diet</td>
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<td>IGF-1</td>
<td>Insulin-like Growth Factor 1</td>
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<td>IF</td>
<td>Intermittent Fasting</td>
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<td>IL-6</td>
<td>Interleukin 6</td>
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<td>MCI</td>
<td>Mild Cognitive Impairment</td>
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<td>MetS</td>
<td>Metabolic Syndrome</td>
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<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<tr>
<td>NIH</td>
<td>National Institute of Health</td>
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<td>PA</td>
<td>Physical Activity</td>
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<td>T2DM</td>
<td>Type 2 Diabetes Mellitus</td>
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<td>TNF-α</td>
<td>Tumor Necrosis Factor α</td>
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<tr>
<td>WC</td>
<td>Waist Circumference</td>
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<tr>
<td>WHR</td>
<td>Waist-Hip Ratio</td>
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1. Adiposity and Dementia

1.1 Introduction to Cognitive Decline and Dementia

A growing body of epidemiological evidence suggests that obesity may increase risk of dementia, including Alzheimer’s disease, the leading cause of dementia worldwide (Alzheimer’s Association, 2012). In a population that is increasingly obese and rapidly aging, a causal link between obesity and AD would have significant public health implications. A clear understanding of the relationship of obesity to dementia risk is therefore important, but further research is needed before this can be achieved. In particular, there is a need to determine the extent to which timing, duration and extent of obesity affect risk, and the mechanisms by which such risks may be altered.

Alzheimer’s disease (AD) is the 6th leading cause of death in the United States today (Alzheimer’s Association, 2012). It is the leading cause of dementia, accounting for 60-80% of cases (Alzheimer’s Association, 2009). At present, dementia afflicts over 5.4 million Americans, however with the aging population prevalence is likely to increase to 6.7 million by 2025, and 13.5 million by 2050 if nothing is done to prevent it (Alzheimer’s Association, 2012; Herbert, Beckett, Scherr, & Evans, 2001). Globally, the direct and indirect costs of dementia were estimated to total US$ 604 billion in 2010, or 1% of the aggregated worldwide GDP (World Health Organization, 2012). In the same year, costs of dementia in the United Kingdom (£23 billion) almost matched those of cancer (£12 billion), heart disease (£8 billion) and stroke (£5 billion) combined (World Health Organization, 2012). In the United States, Medicare, Medicaid and out-of-pocket payments for dementia health care, long-term care, and hospice care were estimated to be $200B, while caregivers, primarily family members, provided an estimated 17.4B hours of unpaid care valued at $210B (Alzheimer’s Association, 2012). Furthermore, the physical and emotional impact of dementia care giving was estimated to result in $8.7B in
increased healthcare costs in the United States in 2011 (Alzheimer’s Association, 2012). These costs do not account for the devastating emotional and personal costs of dementia for caregivers and patients.

Dementia refers to a group of conditions characterized by a decline in memory and at least one other cognitive function that are severe enough to impair activities of daily living (Alzheimer’s Association, 2009). Affected cognitive functions include a wide variety of processes necessary for thinking, planning and action, including functions such as memory, attention, or executive function. Dementia can be caused by a number of different conditions, of which dementia of the Alzheimer’s type is just one. Vascular dementia (VaD), is another type of dementia, caused by cerebrovascular incidents, which accounts for 5-15% of all cases of dementia in the United States (Alzheimer’s Association, 2012). Other types of dementia, such as frontotemporal dementia (FTD) and dementia with lewy bodies, make up the remainder of dementia cases.

Alzheimer’s disease is unique among the 10 leading causes of death in that there are currently no effective treatments for the underlying pathology, and no options for prevention. Since age is a primary risk factor, the development of primary prevention strategies to delay the onset of AD by 5 years could result in an estimated 57% reduction in the number of persons with AD in the United States, and reduce the projected Medicare costs of AD from $627 to $344 billion (Sperling et al., 2011). However there is a clear need to better understand the factors that contribute to the disease, particularly early risk factors and pathophysiology, before successful interventions can be developed. This has been highlighted by the lack of efficacy of clinical trials directed at treating AD pathophysiology in persons already clinically diagnosed with dementia. The lack of success may reflect the difficulty of reversing the neurological damage already done
by this late stage of the disease, rather than the appropriateness of the target. Intervening earlier in the disease process may have better success.

Hence we need to better understand the disease process at pre-clinical stages of the disease (Sperling et al., 2011). At present formal diagnosis of AD can be made on autopsy, and is confirmed by the presence of hallmark pathology - neuritic β-amyloid plaques and tau tangles in the brain (Budson & Solomon, 2011). However although a correlation between these pathological features and cognitive function is observed (Riley, Snowdon, Desrosiers, & Markesbery, 2005), some persons who show these pathological markers never develop clinical symptoms of dementia in their lifetime (Riley et al., 2005), indicating that factors other than the presence of plaques and tangles themselves may be involved. By contrast clinical diagnosis of AD is currently based on severity of behavioral and cognitive symptoms. No biomarkers have yet been found to be reliable markers of the disease, so clinical diagnosis occurs once cognitive impairments have become so severe that they interfere with activities of daily living (McKhann et al., 2011).

1.1.1 Pre-clinical Stages of Alzheimer’s Disease

The search for points of early intervention may be assisted by the growing recognition that pre-clinical signs of the disease are apparent years, or even decades, before clinical diagnosis (Jack et al., 2011; Sperling et al., 2011). These findings have been made possible by a combination of factors. Advances in neuroimaging have made structural, neurochemical and functional alterations in the brains of asymptomatic persons apparent, and evidence of potential biomarkers of pathology in pre-clinical persons also continues to build (Jack et al., 2011; Sperling et al., 2011). Many longitudinal studies have also contributed to the growing awareness of subtle cognitive alterations many years before clinical diagnosis (Sperling et al., 2011). Together, these advances, and the lack of success in treating symptomatic AD, have
contributed to an awareness of the need to look for modifiable pre-clinical processes during mid-adulthood that could contribute to modification of disease pathology. Epidemiological evidence, discussed in detail in section 1.3, suggests that midlife obesity may be one such pre-clinical risk factor contributing to disease pathology.

What precedes clinically diagnosable dementia? Evidence of a gradual progression of cognitive decline is now apparent, though the rate of progression varies considerably between individuals (Sperling et al., 2011).

Alzheimer’s disease is preceded by the clinically diagnosable state of Mild Cognitive Impairment (MCI), which is now increasingly viewed as a prodromal stage of dementia (Albert et al., 2011) (Budson & Solomon, 2011; Sperling et al., 2011). MCI can be diagnosed when declines in memory or other cognitive functions are clinically detectable, but not severe enough to interfere with activities of daily living (Albert et al., 2011). Many older adults do not seek medical attention at this stage, but it is estimated that 10-20% of adults older than 65 years have MCI (Alzheimer’s Association, 2009). Prognosis for those diagnosed with MCI varies. A small minority of individuals regain normal cognitive function, and some others maintain their mild impairment (Bennett et al., 2002). However MCI has a high risk of progression to dementia, particularly dementia of the Alzheimer’s type. It is estimated that in the community the conversion rate from MCI to dementia is about 5-10% per year (Etgen, Bickel, & Forstl, 2010) Rates may be higher among clinical populations presenting with memory complaints.

Prior to diagnosable MCI, subtle cognitive declines may also become gradually apparent in pre-clinical populations (Jack et al., 2011; Sperling et al., 2011). Cognitive decline involves decreased function from prior levels in one or more cognitive domains. With cognitive function defined as the capacity for abilities such as attention, memory, perception, self-volition, language and judgment (Anderson & McConnell, 2007). A small amount of cognitive decline is a
normal part of aging (Budson & Solomon, 2011), and subjective complaints about memory and other cognitive functions increase with advancing age (Newson & Kemps, 2006), however for some the extent of decline across midlife and into old age is greater than would be expected in normal cognitive aging.

Figure 1.1.1. A gradual process of pre-clinical cognitive decline typically precedes Alzheimer’s disease.
### Table 1.1. Cognitive function and cognitive impairments defined.

<table>
<thead>
<tr>
<th>Cognitive function</th>
<th>The capacity for thinking, planning and acting, including functions such as attention, memory, self-volition, language and judgment.</th>
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<tr>
<td>Neurocognitive health</td>
<td>Healthy brain and cognitive function.</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>A generic term referring to any impairment in cognitive function/s.</td>
</tr>
<tr>
<td>Mild Cognitive Impairment (MCI)</td>
<td>A clinical diagnosis involving impairment in one or more cognitive functions greater than would be expected for the person’s age and education (Albert et al., 2011).</td>
</tr>
<tr>
<td>Dementia</td>
<td>A group of conditions characterized by significant declines in memory and/or other cognitive functions that are severe enough to affect activities of daily living (McKhann et al., 2011).</td>
</tr>
<tr>
<td>Alzheimer’s disease (AD)</td>
<td>Dementia of the Alzheimer’s Type (DAT) is the development of memory impairment and at least one other cognitive disturbance, that each cause significant impairment and represent a decline from prior functioning (APA, 2000).</td>
</tr>
<tr>
<td>Vascular dementia (VaD)</td>
<td>The development of memory impairment and at least one other cognitive disturbance, with evidence of cerebrovascular disease (APA, 2000)</td>
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### 1.2 A Lifecourse Approach to Alzheimer’s Disease

The emerging evidence of a long trajectory for AD pathology (Sperling et al., 2011) and cognitive decline suggests that this may be a disease developed over a lifetime, rather than a disease of old age (Gustafson, 2008). Hence a lifecourse approach to AD could be useful. (Kuh & Ben-Shlomo, 2004). As already noted, significant cognitive decline with advancing age is not a normal part of aging, and most older adults retain excellent neurocognitive function late in their lives (Alzheimer’s Association, 2012). However age is the leading risk factor for AD. Most cases of dementia are diagnosed after the age of 65 (Alzheimer’s Association, 2012; Budson & Solomon, 2011). This raises an important question: what differentiates people who experience healthy cognitive aging from those who experience significant cognitive decline and eventual dementia? Genetic research indicates that for most people genes contribute to only a small
proportion of the difference (Alzheimer’s Association, 2012). This leaves a significant role for social and environmental exposures across the lifespan.

1.2.1 The Lifecourse Approach to Chronic Disease

The lifecourse approach (Kuh & Ben-Shlomo, 2004) is widely used to understand the etiology of chronic diseases. As described by (Kuh & Ben-Shlomo, 2004), exposures throughout the lifespan can influence both the incidence of chronic disease and its course. Sensitivity to risk factors may vary across the lifespan. This can lead to different patterns of risk-outcome relationships, such as those summarized in Table 1.2.1 below (Glymour & Manly, 2008; Power & Hertzman, 1997; Wadsworth, 1997). These models of exposure are not mutually exclusive, but can interact to shape health outcomes, with effects that could become increasingly apparent with advancing age.
Table 1.2.1. Some potential exposure-outcome relations suggested by the lifecourse approach.
Adapted from (Glymour & Manly, 2008; Power & Hertzman, 1997; Wadsworth, 1997)

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate risk model</td>
<td>Short period between exposure and health outcome.</td>
</tr>
<tr>
<td></td>
<td>Return to baseline health after removal of risk factor.</td>
</tr>
<tr>
<td></td>
<td>E.g. Delirium in hospitalized older adults can be reversed by medication management (Gray, Lai, &amp; Larson, 1999).</td>
</tr>
<tr>
<td>Cumulative model</td>
<td>Each exposure leads to some harm.</td>
</tr>
<tr>
<td></td>
<td>The cumulative effect of exposures increases disease risk.</td>
</tr>
<tr>
<td></td>
<td>Removal of exposure does not reverse harm already done.</td>
</tr>
<tr>
<td></td>
<td>E.g. Effects of lead exposure over time impairs older adults’ cognitive function (Weisskopf et al., 2004).</td>
</tr>
<tr>
<td>Latency model</td>
<td>Exposure during a critical period of development increases risk of disease much later in life, but health effects may not be immediately apparent.</td>
</tr>
<tr>
<td></td>
<td>E.g. Poverty in early life may provide an early exposure to stress that increases vulnerability to cognitive decline later in life (Lupien, King, Meaney, &amp; McEwen, 2000)</td>
</tr>
<tr>
<td>Social trajectory model</td>
<td>Exposure sets in motion a succession of adverse social events that increase vulnerability later in life.</td>
</tr>
<tr>
<td></td>
<td>E.g. Poverty early in life may reduce educational access, which reduces education attainment and opportunities for mentally stimulating occupations, which may increase risk of cognitive decline and dementia later in life (Al Hazzouri, Haan, Whitmer, Yaffe, &amp; Neuhaus, 2012).</td>
</tr>
</tbody>
</table>

1.2.2 Applying the Lifecourse Approach to Cognitive Aging

With its emphasis on understanding the timing of exposures, the lifecourse approach could provide a useful framework to investigate factors differentiating healthy cognitive aging from cognitive decline or dementia. Cognitive aging has not been a prominent focus for lifecourse epidemiology (Glymour & Manly, 2008). However the lifecourse approach suggests that differences in cognitive function between individuals of the same age may reflect a range of
detrimental or neuroprotective biological, psychological and social exposures experienced in early and mid-adulthood (Stein & Moritz, 1999), and as a person ages, the cumulative effects of these exposures could bring widening differences in cognitive function, as depicted in Figure 1.2.1 below.

As indicated in the four exposure-outcome models summarized in Table 1.2.1, investigation of the effects of risk factors for AD will require careful attention to the timing and duration of exposure. An exposure may be detrimental during sensitive periods of development, with effects that do not become apparent for many years, or which only appear when combined with another later exposure. For example it remains possible that exposure to obesity in late life alone does not confer additional risk for dementia, but exposure to maternal obesity while in utero, or exposure to childhood obesity during critical periods of neural development, increase risk of dementia much later in life (latency model). It is also possible that prolonged duration of

Figure 1.2.1. As people age, the cumulative effects of damaging and protective exposures may lead to widening differences in cognitive function.
obesity during early and mid-adulthood could contribute cumulative damage to the brain over many years (cumulative model), and that the duration of exposure acquired by older adults who become obese in their old age is insufficient to confer significant risk. It is beyond the scope of this dissertation to address the effects of obesity across the entire lifespan. Instead, this paper will focus on investigating factors consistent with a cumulative model. It will therefore focus on factors that could have cumulative effects on the neural and cognitive health of adults in early and mid-adulthood. This time period could correspond to the pre-clinical stages of AD in affected persons and so reflect early-stage risk factors for later cognitive decline with advancing age.

1.2.3 Evidence for Modifiable Risk Factors in Midlife

A number of factors have recently emerged that could potentially act as midlife risk factors for AD later in life. These include Type 2 diabetes mellitus, the metabolic syndrome and hypertension. Obesity is causally related to each of these conditions, and so has the potential to the underlying pathological process.

Evidence indicates that Type 2 diabetes mellitus (T2DM), a chronic disease characterized by insulin resistance and glucose dysregulation, increases the risk of MCI and dementia (Biessels & Gispen, 2005; Whitmer, Karter, Yaffe, Quesenberry, & Selby, 2009; Yaffe et al., 2004a). It is well-known that people with diabetes have increased risk of micro-vascular complications (e.g. neuropathy, retinopathy, nephropathy, and macrovascular events (myocardial infarction, stroke), and are therefore at increased risk for vascular dementia. However there also seems to be an independent risk of developing AD. Type 2 diabetes mellitus can also have adverse effects on general cognitive function earlier in life, in the absence of clinically diagnosed MCI or AD (Cukierman, Gerstein, & Williamson, 2005; Elias, Elias, Sullivan, Wolf, & D'Agostino, 2005). Both men and women with T2DM show deficits in attention, processing speed, memory, and
executive functioning (Biessels, ter Braak, Erkelens, & Hijman, 2001; Biessels & Gispen, 2005; Manschet et al., 2007; Messier, 2005; Ostrosky-Solis, Mendoza, & Ardila, 2001; Yaffe et al., 2004b). The association has been found in cross-sectional (Messier, 2005; Ryan, 2005; Strachan, Deary, Ewing, & Frier, 1997) and prospective follow-up studies (Cukierman et al., 2005; Elias et al., 2005; Messier, 2005). In addition, intervention studies using insulin-sensitizing agents have had some success in reducing cognitive decline (Craft et al., 2003; Craft et al., 2012). Though these findings are not universal, systematic reviews of prospective studies to date (Cukierman et al., 2005), and a growing professional consensus, indicates that the consistency and strength of the evidence is sufficient to warrant including cognitive decline as one of the potential complications of diabetes (Plassman, Williams, Burke, Holsinger, & Benjamin, 2010).

Several studies also report that the Metabolic Syndrome (MetS) independently increases risk of cognitive decline and incident dementia (Yaffe, 2007; Yaffe et al., 2004c). According to the criteria of the International Diabetes Federation (IDF, 2006), the MetS is defined as having central obesity and any two of the following: raised triglycerides (> 150 mg/dL), reduced HDL cholesterol (< 40 mg/dL), raised blood pressure (systolic BP > 130 or diastolic BP >85 mm Hg), or raised fasting glucose (>100 mg/dL), or treatment for previous diagnosis of any of those conditions. Since the combination of components can vary it is possible that different components confer independent risk of cognitive decline. Consistent with this, non-diabetic individuals with insulin resistance also show some evidence of deficits in learning and memory (Vanhanen et al., 1997; Vanhanen et al., 2006), even after controlling for vascular factors (Convit, Wolf, Tarshish, & de Leon, 2003).

An emerging body of evidence now suggests an association between obesity and increased risk of cognitive decline and dementia (Cournot et al., 2006a; Gustafson, 2006; Whitmer, 2007; Whitmer, Gunderson, Quesenberry, Zhou, & Yaffe, 2007). Obesity is a risk factor
for T2DM and all components of the MetS (Abbasi, Brown, Lamendola, McLaughlin, & Reaven, 2002; Boyko et al., 2000; Zimmet, Boyko, Collier, & Courten, 1999), and may play a causal role in many of the clinical features of these conditions. Obesity already contributes to over 300,000 deaths per year in the United States alone (Boeka & Lokken, 2008), and rates of obesity have risen dramatically across the population over the past 20 years. The majority of the population who have experienced these weight gains have yet to reach the ages at which AD is most likely to manifest. Hence if obesity does contribute even a small increase in risk of dementia, the implications at a population level could be particularly significant for an aging and increasingly obese population. Therefore the goal of this dissertation is to investigate whether obesity affects adult neurocognitive health, as well as the potential that behavioral interventions directed at reducing obesity or mitigating its effects could improve adult neurocognitive health.

Towards these ends the author and colleagues conducted 3 studies. **Study 1** involved a systematic review of the published empirical evidence linking weight or adiposity to adult cognitive function. **Study 2** investigated the association between adiposity and cognitive function in the general population. **Study 3** involved a systematic review of the published empirical data on interventions for weight loss, and their effects on human cognitive function. Finally, **study 4** investigated the effects of weight loss diets on the cognitive function of obese adults.

### 1.3 Study 1. Weight and Cognitive Health: A Systematic Literature Review

#### 1.3.1 Introduction

Alzheimer’s disease is the leading cause of dementia and the 6th leading cause of death in the United States today (Alzheimer’s Association, 2012). It afflicts over 5.4 million Americans today, and prevalence is likely to increase to 6.7 million by 2025 (Herbert et al., 2001). There is
currently no effective treatment, but evidence for modifiable risk factors is emerging. Among these, several recent studies have linked obesity to increased risk of cognitive decline and dementia (Cournot et al., 2006a; Gustafson et al., 2009; Gustafson, Lissner, Bengtsson, Bjorkelund, & Skoog, 2004; Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005). If obesity contributes even a small increase in risk of dementia, the effects across the increasingly obese populations of Western nations could be significant. The purpose of this review is therefore to systematically investigate the evidence from prospective studies that obesity increases risk of cognitive decline or dementia.

Obesity is a significant excess of body fat, or adipose tissue, often defined as a Body Mass Index (BMI, kg/m$^2$) greater than 30. The BMI is a simple but useful measure that allows a general estimation of adiposity; however it cannot accurately reflect the proportion of adipose tissue carried by an individual. It is likely that adiposity, rather than weight, would mediate any effect of obesity on neurocognitive health, for adipose tissue is not just a storage depot for fat, but is also endocrinologically and immunologically active. Adipocytes secrete various active metabolites that could cross the blood-brain barrier (BBB) to affect brain health. Central adipose tissue, distributed around the trunk and including subcutaneous and omental adipose reserves, is known to be particularly active in this regard, secreting numerous adipokines such as leptin, and cytokines (Bastard et al., 2000; Bastard et al., 2006; Fain, 2006; Ingvartsen & Boisclair, 2001; Wellen & Hotamisligil, 2003). In addition, obesity is related to many other vascular and metabolic factors implicated in AD pathology, including insulin resistance and hypertension.

It is important to discover the age/s at which obesity might have its greatest impact on neurocognitive health since, according to the lifecourse approach (Kuh & Ben-Shlomo, 2004), the age at which an exposure is encountered can have a significant effect on outcome. There may be some evidence for modifiable exposures early in life contributing to late life dementia.
risk. For example, some studies have investigated the association between childhood obesity and adult cognitive function. (Lupien et al., 2000; Miller et al., 2009). It is beyond the scope of this paper to address all the evidence across the lifespan. We will therefore focus this review on the risk of adult obesity for risk of cognitive decline and dementia in late life, where the exposure is most proximal to potential “pre-clinical” stages of dementia (Sperling et al., 2011).

Among adults, it remains important to account for the age at which obesity was measured, the measure of adiposity used, and the age of cognitive outcomes (Gustafson, 2008; Whitmer et al., 2007). These are important for two main reasons: 1) because of the effects of aging on body composition, and 2) because of the tendency for weight loss in clinical and subclinical dementia.

Firstly, advancing age commonly brings significant changes in body composition, even if overall weight does not change. Muscle mass often declines, and adipose tissue often increases with increasing age (Miller & Wolfe, 2008). For this reason, BMI can be a poor estimate of adiposity for older adults, as it cannot differentiate fat free mass from adipose tissue. Thus studies measuring the association between BMI in older adults and dementia cannot rule out the possibility that someone who has a healthy BMI is actually carrying a relatively large fat mass, having lost significant bone density and muscle mass. Similarly, studies comparing BMI across multiple ages cannot address the potential for loss of fat-free mass with advancing age. This may be a significant confounding factor for studies that rely on BMI alone, particularly among older adults.

Secondly, measurement of the association between weight and cognitive function among older adults can be complicated by the tendency of persons with dementia to lose significant amounts of weight as part of the disease (Wirth, Bauer, & Sieber, 2007). This observation has been reported in many observational and clinical studies of dementia (Berlinger
Weight loss may occur shortly before dementia diagnosis (Johnson et al., 2006), so that on clinical presentation, the person with dementia is more likely to be underweight than overweight (Gorospe & Dave, 2007). The weight loss that occurs in dementia could possibly occur because of neural damage to appetite and self-regulation regions of the brain, dysregulated circadian rhythm, or dysregulated behavior more generally. As a result, cross-sectional studies of weight and dementia, or longitudinal studies among older adults with short follow-up periods, could give the impression that persons who are overweight or obese in old age have lower dementia risk (Dahl, Lopponen, Isoaho, Berg, & Kivela, 2008a), no matter what measure of adiposity was used.

While a number of other reviews have indeed taken these factors into account (Anstey, Cherbuin, Budge, & Young, 2011; Dahl & Hassing, 2012; Gorospe & Dave, 2007; Luchsinger & Gustafson, 2009; Naderali, Ratcliffe, & Dale, 2009; Yen, 2005), this review differs from other recent reviews in that it is a systematic review that attempts to provide a comprehensive snapshot of all longitudinal studies on weight, adiposity and adult cognitive health outcomes available through MEDLINE and PsychINFO. Other reviews have limited their searches to studies of AD, only studies with specific follow-up periods (Beydoun, Beydoun, & Wang, 2008; Dahl & Hassing, 2012), only studies that included at least 2 cognitive domains rather than diagnoses of dementia or global screening instruments (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009)), used either Medline or PubMed but not both (Beydoun et al., 2008; van den Berg et al., 2009) or were not systematic reviews (Gustafson, 2006; Luchsinger, Patel, Tang, Schupf, & Mayeux, 2008; Naderali et al., 2009; Whitmer, 2007).
1.3.2 Methods

**Literature Search Terms and Study Inclusion Criteria**

English-language articles focused on weight or adiposity and cognition or dementia outcomes were identified using MEDLINE and PsycINFO. The following search terms were used in various combinations: dementia, Alzheimer’s disease, cognition disorders, cognitive decline, cognitive impairment, cognition, cognitive function, and cognitive health, as well as obesity, overweight, weight, fat, adiposity, central obesity, visceral obesity, visceral adiposity, waist-hip ratio, and waist circumference. All relevant articles published up until January 30th, 2013, and retrievable by university library search or interlibrary loan were considered for this systematic review. Reference lists of all potentially eligible articles were reviewed to ensure inclusion of all relevant literature.

To be included in this review, the articles had to meet the following eligibility criteria: empirical articles that are available via university libraries or interlibrary loan, written in English, and included the weight/adiposity and dementia/cognition related search terms above within the title, abstract, and/or keywords. Studies of weight in childhood or adolescence were considered eligible if they included adult cognitive outcomes. Studies of change in weight or weight outcomes in a population that began with dementia at baseline were excluded. Similarly studies focused on health outcomes for other cognitively impaired persons with a medical or psychiatric diagnosis known to cause cognitive impairment, such as developmental disability, schizophrenia, bipolar disorder or traumatic brain injury, were excluded. Studies with a specific focus on eating disordered populations were also excluded, as were other studies focused on specific medical or psychiatric populations. Dissertations, reviews, opinions, theoretical papers or editorials were excluded from this review.
Article Selection and Abstraction

A three-step process guided assessment and selection of articles. First, the study author reviewed the titles and abstracts of all potential articles retrieved by the search terms, identifying the set of article abstracts that potentially matched the eligibility criteria. Second, the study author reviewed in-depth the abstracts and full articles for studies whose abstracts passed the first review for inclusion. Information from the full articles were entered into summary tables. From this set the author identified the set of full articles which matched the eligibility criteria below. Finally, reference lists of eligible articles were reviewed for additional relevant articles to potentially include. These articles were also assessed for eligibility through a two step process.
1.3.3 Results

Number of Articles Included in Review

A total of 4320 articles were identified using the search terms. Of these articles, 4085 were excluded after a preliminary review of title and/or abstract because they were not relevant and/or did not meet the inclusion criteria (e.g. topic was relevant but the article was an editorial). The remaining 235 full articles were then reviewed and abstracted by the study author. Of these 235 articles, 64 observational studies were considered eligible after more thorough review, and were therefore included in this study. Included articles were then categorized according to study population (persons with dementia, cognitive impairment, or a study of cognitive function more generally. Articles were further categorized by whether their
results supported or opposed a link between adiposity and cognitive health outcomes, and age at which weight and cognitive outcomes were measured. A flow chart of the sorting and inclusion process can be seen in Figure 1.3.1.

| Table 1.3.1. Summary of results for the obesity and cognitive function literature review. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | FOR AN ASSOCIATION | AGAINST AN ASSOCIATION |
| Dementia                        | Midlife          | Older adults | Midlife          | Older adults | |
| Midlife                         | 61% (11)         | 39% (7)      | 20% (4)          | 80% (16)     |
| Older adults                    | 39% (7)          |              | 20% (4)          | 80% (16)     |
| MCI                             | Na               | na           | 0%               | 100% (5)     |
| Cognitive Function              | 71% (10)         | 29% (4)      | 31% (4)          | 69% (9)      |
| Central obesity                 | 55% (6)          | 45% (5)      | 17% (2)          | 83% (10)     |

**Articles Assessing Dementia Risk**

Among the 38 longitudinal studies in which dementia was the principle cognitive outcome, 18 reported evidence supporting an association between obesity and increased risk dementia. Of these, 15 reported specific results for the diagnosis of AD. In contrast, 20 studies reported no association between obesity and dementia. Of these, 9 reported specific results for a diagnosis of AD. The results are shown in Table 1.3.2 and Table 1.3.3.

**Supporting an association between obesity and dementia:** Among the 18 studies finding a significant association between higher weight/adiposity and increased dementia risk, 11 (61%) reported an association between midlife weight measures and increased dementia risk (Beydoun & Beason-Held, 2008; Chiang et al., 2007; Fitzpatrick et al., 2009; Gelber et al., 2012; Gustafson et al., 2009; Hassing et al., 2009; Kivipelto et al., 2005; Rosengren, Skoog, Gustafson, & Wilhelmsen, 2005; Whitmer et al., 2005; Whitmer et al., 2007; Whitmer et al., 2008), while 7 (39%) reported that increased weight later in life (≥ 65 years) increased risk of dementia (Buchman et al., 2005; Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003; Hayden et al., 2006a; Kerwin et al., 2011; Luchsinger, Cheng, Tang, Schupf, & Mayeux, 2012; Luchsinger, Patel, Tang, Schupf, & Mayeux, 2007; Xu et al., 2011). Fifteen of these studies reported outcomes for
AD specifically. All 18 of these studies measured BMI. Only 7 reported BMI with other measures of adiposity such as WHR, WC or percent fat mass.

Opposing an association between obesity and dementia: Twenty longitudinal studies reported evidence that did not support an association between obesity and dementia. Of these studies only 4 (20%) reported adiposity in midlife, while 16 (80%) assessed adiposity in older adults. Only 9 of these studies addressed AD specifically (refs). Among these studies, 13 measured only BMI. Only 6 reported BMI with other measures of adiposity such as WHR, WC or percent fat mass.
### Table 1.3.2. Longitudinal studies supporting an association between overweight and dementia.

#### STUDIES OF MIDLIFE ADIPOSITY

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>Dementia Assessment</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
</table>
| (Beydoun & Beason-Held, 2008) | 2,322  | ≥20          | median 23.4        | BMI, WC           | Dx AD, NINCDS-ADRSA criteria. | Midlife (30, 40 or 45 years):  
- Men: being underweight (BMI <or=18.5) increased the likelihood of AD (HR = 5.76, 95% CI: 2.07, 16.00).  
- Women: being obese (BMI ≥30, WC ≥80th percentile) increased AD risk (HR = 6.57, 95% CI: 1.96, 22.02).  
Women who lost weight (BMI change <10th percentile) between ages 30 and 45 years were also at increased risk (HR = 2.02, 95% CI: 1.06, 3.85).  
Weight gain among men (BMI change >90th percentile) between age 30 and 50 years increased AD risk (HR = 3.70, 95% CI: 1.43, 9.56). |
| (Chiang et al., 2007) | 157 demented cases 628 matched controls | Age 30 and older (1982-1992) | 8-20 years Nested case-control study | BMI (Chinese criteria) | Dx AD, VaD, Chinese version of DSM-IV | A J-shaped relationship was observed between BMI and dementia.  
Compared to BMI -20.5–22.9 , odds (OR) for developing dementia was:  
1.84 (1.02–3.33) for BMI <20.5,  
1.87 (1.08–3.23) for BMI 23.0–25.4,  
and 2.44 (1.39–4.28) for BMI >/=25  
Similar findings were observed for AD and VaD. |
### Table 1.3.2. Longitudinal studies supporting an association between overweight and dementia.

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<th>Author (date)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>(Fitzpatrick et al., 2009)</td>
<td>2798</td>
<td>74.7 (but baseline BMI based on self-report of weight at age 50)</td>
<td>5.4 mean (but much more when compared to self-reported BMI at age 50)</td>
<td>BMI</td>
<td>AD dx: NINCDS-ADRDA criteria; VaD dx: California Alzheimer’s Disease and Treatment Centers criteria</td>
<td>Midlife obesity increased risk of dementia compared to BMI 20-25 healthy weight group (HR 1.39; 95% CI 1.03-1.87). Reversed in assessments of late-life BMI: - Underweight persons (BMI 20) had an increased risk of dementia (HR 1.62; 1.02-2.64), - being overweight (BMI 25-30) was not associated with risk of dementia (0.92; 0.72-1.18) - being obese reduced the risk of dementia (0.63; 0.44-0.91).</td>
</tr>
<tr>
<td>(Gelber et al., 2012)</td>
<td>3468</td>
<td>52</td>
<td>25-28</td>
<td>BMI</td>
<td>Dementia dx: DSM-III-R criteria; AD dx: NINCDS-ADRDA criteria; VaD dx: California Alzheimer’s Disease and Treatment Centers criteria</td>
<td>Compared to BMI &lt;22.6, being overweight or obese (BMI &gt; 25.0) was associated with greater risk of dementia (OR = 1.87, 95% CI = 1.26-2.77)</td>
</tr>
<tr>
<td>(Gustafson et al., 2009)</td>
<td>1462</td>
<td>38-60</td>
<td>32</td>
<td>BMI, WC, WHR</td>
<td>Dementia dx: DSM-III-R criteria; AD dx: NINCDS-ADRDA criteria; VaD dx: NINDS-AIREN criteria</td>
<td>Logistic models showed that a midlife WHR greater than 0.80 more than doubled dementia risk (OR 2.22, 95% CI: 1.00–4.94, p=0.049). Cox models showed no association.</td>
</tr>
<tr>
<td>(Hassing et al., 2009)</td>
<td>1152</td>
<td>45-65 years (mean 52.5)</td>
<td>up to 40</td>
<td>BMI</td>
<td>AD dx: NINCDS-ADRDA criteria; VaD dx: NINDS-AIREN criteria</td>
<td>Overweight in midlife had an elevated risk of - dementia (OR=1.59; 95% CI: 1.21-2.07), - AD (OR=1.71; 95% CI: 1.24-2.35), - VaD (OR=1.55; 95% CI: 0.98-2.47).</td>
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</table>
Table 1.3.2. Longitudinal studies supporting an association between overweight and dementia.

<table>
<thead>
<tr>
<th>Author (date)</th>
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</thead>
<tbody>
<tr>
<td>(Kivipelto et al., 2005)</td>
<td>1449</td>
<td>50.6</td>
<td>Mean 21</td>
<td>BMI</td>
<td>Dx dementia, AD: DSM-IV criteria; AD dx: NINCDS-ADRA criteria</td>
<td>Midlife obesity was associated with late life dementia after adjusting for vascular factors (OR = 1.9, 95% CI: 1.0-4.6).</td>
</tr>
<tr>
<td>(Rosengren et al., 2005)</td>
<td>7402</td>
<td>47 – 55</td>
<td>25 – 28</td>
<td>BMI</td>
<td>Dx Dementia, AD: Death register and hospital discharge diagnoses</td>
<td>J-shaped curve. BMI less than 20 in midlife was associated with increased risk of primary hospital diagnosis of dementia in late life. BMI of ≥22.5 in midlife was associated with increased risk of a primary hospital diagnosis of dementia.</td>
</tr>
<tr>
<td>(Whitmer et al., 2005)</td>
<td>10,276</td>
<td>40 - 45</td>
<td>21 – 39</td>
<td>BMI, skinfold thickness</td>
<td>Dementia dx: ICD-9 codes</td>
<td>Compared with healthy weight: - Obesity in midlife (BMI &gt;= 30) increased risk of dementia 74% (HR 1.74, 95% CI 1.34 to 2.26). - Overweight in midlife (BMI 25.0-29.9) increased risk of dementia 35% (1.35, 1.14 to 1.60). The highest quintile of skinfold thickness had a 72% greater risk of dementia than the lowest quintile (1.72, 1.36 to 2.18, and 1.59, 1.24 to 2.04).</td>
</tr>
<tr>
<td>(Whitmer et al., 2007)</td>
<td>10,136</td>
<td>40-45</td>
<td>26 – 42</td>
<td>BMI</td>
<td>Review of medical records from Neurology visits Dx VaD, AD</td>
<td>Obesity in midlife increased risk of AD (adjHR=3.10, 95% CI 2.19-4.38), and risk of VaD (adjHR=5.01, 95% CI 2.98-8.43) Overweight in midlife increased risk of AD (adj HR=2.09, 95% CI 1.69-2.60) and VaD (HR=1.95, 95% CI 1.29-2.96 for VaD).</td>
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**STUDIES OF MIDLIFE ADIPOSITY**

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<tbody>
<tr>
<td>(Whitmer et al., 2008)</td>
<td>6583</td>
<td>40-45</td>
<td>26 – 42?</td>
<td>BMI, Sagittal Abdominal Diameter (SAD)</td>
<td>ICD-9 codes</td>
<td>Persons in the highest quintile of SAD in midlife had increased risk of dementia (HR, 2.72; 95% CI, 2.33-3.33) compared to persons in the lowest quintile. Those with high SAD (&gt;25 cm) but healthy BMI had an increased risk (HR, 1.89; 95% CI, 0.98-3.81) vs. those with low SAD (&lt;25 cm) and healthy BMI. Persons who were both obese and with high SAD had the highest risk of dementia (HR, 3.60; 95% CI, 2.85-4.55).</td>
</tr>
<tr>
<td>Author (date)</td>
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<tr>
<td>(Buchman et al., 2005)</td>
<td>820</td>
<td>As above</td>
<td>up to 10 (mean 5.5)</td>
<td>BMI</td>
<td>AD dx: NINCDS-ADRD A criteria</td>
<td>A 1-point annual decline in BMI was associated with increased risk of AD compared with persons with no change in BMI (HR 0.730; 95% CI 0.625 to 0.852).</td>
</tr>
<tr>
<td>(Gustafson et al., 2003)</td>
<td>392</td>
<td>70</td>
<td>18</td>
<td>BMI</td>
<td>Dementia dx: DSM-III-R criteria; AD dx: NINCDS-ADRD A criteria; VaD dx: NINDS-AIREN criteria.</td>
<td>For every 1.0 increase in BMI at age 70 years, AD risk increased by 36% (Hazard Ratio, 95% CI). These associations were not found in men.</td>
</tr>
<tr>
<td>(Hayden et al., 2006b)</td>
<td>3264</td>
<td>≥65</td>
<td>3.2</td>
<td>BMI</td>
<td>AD dx using NINCDS-ADRD A criteria; VaD dx using NINDS-AIREN criteria</td>
<td>Obesity increased the risk of AD in females (adjHR 2.23, 95% CI 1.09-4.30) but not males.</td>
</tr>
<tr>
<td>(Kerwin et al., 2011)</td>
<td>7163</td>
<td>65 to 80</td>
<td>up to 8 average 4.4</td>
<td>WHR, BMI</td>
<td>3MSE</td>
<td>Central obesity was what mattered. Women with a WHR of ≥0.80 and a BMI of 20.0 - 24.9 had a greater risk of cognitive impairment and probable dementia than more-obese women or women with a WHR less than 0.80. However women with a WHR less than 0.80 and a BMI of 20.0 to 24.9 kg/m2 had poorer scores on cognitive assessments.</td>
</tr>
<tr>
<td>(Luchsing er et al., 2007)</td>
<td>893 BMI, 907 WC, 709 weight</td>
<td>≥65</td>
<td>5</td>
<td>BMI, WC, weight</td>
<td>Dementia dx: DSM-IV criteria; AD dx: NINCDS-ADRD A criteria</td>
<td>In persons &lt;76 years the association between BMI and dementia resembled a U shape, meaning that both low BMI and high BMI increased risk of dementia. In those ≥76 years, dementia risk decreased with higher BMI. In persons &lt;76 years, the highest quartile of WC correlated to dementia and AD risk. Weight loss was related to a higher risk of dementia and dementia associated with stroke DAS). Weight gain was related to a higher DAS risk only.</td>
</tr>
</tbody>
</table>
### Table 1.3.2. Longitudinal studies supporting an association between overweight and dementia.

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>Dementia Assessment</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Luchsinger et al., 2012)</td>
<td>1459</td>
<td>≥65</td>
<td>7</td>
<td>BMI, WHR, WC</td>
<td>AD dx - NINCDS-ADRDA criteria</td>
<td>Only higher WHR was related to higher AD risk, with the highest quartile of WHR increasing risk 2.5 times compared to the lowest quartile (HR = 2.5; 95% CI = 1.3 - 4.7).</td>
</tr>
<tr>
<td>(Xu et al., 2011)</td>
<td>8,534</td>
<td>43.4 mean</td>
<td>~30</td>
<td>BMI</td>
<td>MMSE, CERAD, Memory in Reality test Dx dementia, VaD, AD</td>
<td>Higher midlife BMI was associated with an increased risk of dementia (OR 1.08, 95% CI 1.03–1.14)</td>
</tr>
</tbody>
</table>
Table 1.3.3. Longitudinal studies not supporting an association between overweight and dementia.

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>Dementia Assessment</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Chen et al., 2010)</td>
<td>286</td>
<td>20s &amp; 40s</td>
<td>~50yr case-control study</td>
<td>BMI</td>
<td>MMSE dx AD: NINCDS-ADRDA criteria; Dx VaD: NINDS-AIREN criteria</td>
<td>Men and women with low BMI in midlife had increased risk of AD (OR = 2.62-3.97, 95% CI) and VaD (OR = 6.23-11.11) compared with those with healthy BMI. High BMI in midlife was associated with increased VaD risk (OR = 15.29 and 10.32) among women.</td>
</tr>
<tr>
<td>(Rosengren et al., 2005)</td>
<td>7402</td>
<td>47 - 55</td>
<td>25-28</td>
<td>BMI</td>
<td>Dementia dx: Death register and hospital discharge diagnoses</td>
<td>J-shaped curve. BMI less than 20 in midlife was associated with increased risk of primary hospital diagnosis of dementia in late life. BMI of ≥22.5 in midlife was associated with increased risk of a primary hospital diagnosis of dementia.</td>
</tr>
<tr>
<td>(Stewart et al., 2005)</td>
<td>1890</td>
<td>46 - 68</td>
<td>32</td>
<td>Weight</td>
<td>Dementia dx: DSM-III-R15 Criteria; AD dx: NINCDS-ADRDA criteria; dx VaD: California Alzheimer Disease and Treatment Centers criteria</td>
<td>Groups that developed and did not develop dementia did not differ with respect to baseline weight or change in weight from mid to late life.</td>
</tr>
<tr>
<td>(Strand et al., 2013)</td>
<td>48,793</td>
<td>35-50</td>
<td>31-35</td>
<td>BMI</td>
<td>Dx dementia, AD: Norwegian Cause of Death Registry</td>
<td>Low BMI (&lt;20 vs. BMI 20-25) in midlife was associated with increased risk of dementia death (HR = 1.76, 95% CI 1.15-2.68).</td>
</tr>
</tbody>
</table>
### Table 1.3.3. Longitudinal studies not supporting an association between overweight and dementia.

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>Dementia Assessment</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Abellan van Kan et al., 2012)</td>
<td>647</td>
<td>≥75</td>
<td>7</td>
<td>Total fat mass (DXA)</td>
<td>SPMSQ</td>
<td>Total fat mass was not significantly associated with dementia risk.</td>
</tr>
<tr>
<td>(Atti et al., 2008)</td>
<td>646</td>
<td>≥75</td>
<td>9</td>
<td>BMI</td>
<td>MMSE; Dementia dx - DSM-III criteria</td>
<td>Persons with a BMI of ≥25.0 had a lower risk of dementia than those with a BMI of 20.0 to 24.9 (HR = 0.75, 95% (CI) = 0.59-0.96),</td>
</tr>
<tr>
<td>(Barrett-Connor, Edelstein, Corey-Bloom, &amp; Wiederholt, 1996)</td>
<td>299</td>
<td>50-79</td>
<td>16-21</td>
<td>Weight</td>
<td>Dx AD neurological test scores, physical examination</td>
<td>Men who developed AD weighed slightly more at baseline (1972-74) than men who remained cognitively intact (( P = .03 )); baseline weights did not differ in women by dementia status (( P = .54 )). Both men and women who were later diagnosed with AD had decreasing weight measured across the three time points (( P &lt; .001 ) for men and ( P &lt; .003 ) for women), whereas men and women who were diagnosed as cognitively intact had no significant change in their weights.</td>
</tr>
<tr>
<td>(Dahl et al., 2008a; Dahl, Lopponen, Isoaho, Berg, &amp; Kivela, 2008b)</td>
<td>605</td>
<td>65-92</td>
<td>8</td>
<td>BMI</td>
<td>Dementia dx DSM-IV criteria.</td>
<td>Women with high BMI scores had a lower dementia risk (HR = 0.90, 95% CI = 0.84-0.96). Trend for men with high BMI scores to have a lower dementia risk, (HR = 0.95, 95% CI = 0.84-1.07).</td>
</tr>
<tr>
<td>(Forti et al., 2010)</td>
<td>749</td>
<td>≥65</td>
<td>3-5</td>
<td>Metabolic Syndrome (MetS) WC</td>
<td>MMSE Dx VaD, AD</td>
<td>In participants aged 75 and older, abdominal obesity was associated with a lower risk of overall dementia (HR = 0.53, 95% CI = 0.28-0.98).</td>
</tr>
</tbody>
</table>
### Table 1.3.3. Longitudinal studies not supporting an association between overweight and dementia.

#### STUDIES OF ADIPOSITY IN OLDER ADULTS

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>Dementia Assessment</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Gao et al., 2011)</td>
<td>1331</td>
<td>≥ 65</td>
<td>mean 6.4</td>
<td>BMI</td>
<td>dx dementia using ICD-10 and DSM-III-R</td>
<td>Greater decline in BMI was associated with greater risk of dementia or MCI (p = .02 for dementia, p = .04 for MCI). BMI in participants with incident dementia, MCI, and normal cognition did not differ 9-12 years before diagnosis. Six years before diagnosis, participants with incident dementia or MCI had significantly lower BMI than participants with normal cognition.</td>
</tr>
<tr>
<td>(Han et al., 2009)</td>
<td>721</td>
<td>60-85</td>
<td>2</td>
<td>BMI, WHR, WC, PBF</td>
<td>CERAD-Korean version Dementia dx using DSM-IV criteria</td>
<td>The change in cognitive function in the elderly was associated with the baseline assessment of BMI, WC, and % body fat. Men who were obese (WHR, BMI) at baseline and subsequently increased weight had improved cognitive function. Women with high WHR at baseline and a subsequent decrease in adiposity had increased risk of cognitive decline. Women with normal WC at baseline and subsequent increased adiposity also had increased risk of cognitive decline.</td>
</tr>
<tr>
<td>(Hughes, Borenstein, Schofield, Wu, &amp; Larson, 2009)</td>
<td>1478</td>
<td>mean 71.8</td>
<td>mean 7.8</td>
<td>BMI</td>
<td>dx VaD, AD, DSM-IV criteria</td>
<td>Higher baseline BMI was significantly associated with a reduced risk of AD (adj HR] = 0.56, 95% [CI] = 0.33–0.97). Slower rate of decline in BMI was associated with a reduced risk of dementia (HR = 0.37, 95% CI= 0.14–0.98), with the association stronger for those who were overweight or obese (HR=0.18, 95% CI=0.05-0.58) compared to normal or underweight (HR=1.00, 95% CI=0.18–5.66) at baseline.</td>
</tr>
</tbody>
</table>
### Table 1.3.3. Longitudinal studies not supporting an association between overweight and dementia.

#### STUDIES OF ADIPOSITY IN OLDER ADULTS

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>Dementia Assessment</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Johnson et al., 2006)</td>
<td>449</td>
<td>65-95</td>
<td>Mean 6</td>
<td>Weight</td>
<td>AD dx - Clinical Dementia Rating Scale</td>
<td>Among older adults, rate of weight loss doubled about 1 year before dementia diagnosis among individuals who developed AD.</td>
</tr>
<tr>
<td>(Knopman, Edland, Cha, Petersen, &amp; Rocca, 2007)</td>
<td>481</td>
<td>At time of onset, 6.1% under age 70 years, 75.6% ages 70 to 89 years, and 18.2% age 90 years or older</td>
<td>Case-Control ~30 years</td>
<td>Weight</td>
<td>DSM-IV criteria applied to medical records</td>
<td>There were no differences in weight between cases and controls 21 to 30 years prior to the onset of dementia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>However starting from 11 – 20 years prior to the index year, women with dementia had lower weight than controls, and the difference increased over time.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>There was a trend for increasing risk of dementia with decreasing weight in women 9 to 10 years before the index year (p = 0.001).</td>
</tr>
<tr>
<td>(Nourhasemi et al., 2003)</td>
<td>3646</td>
<td>≥ 65</td>
<td>8</td>
<td>BMI</td>
<td>MMSE Dx Dementia, AD by DSM-III-R criteria</td>
<td>The risk of dementia was highest for those with a BMI &lt;21 (RR=1.48, CI=95%: 1.08-2.04) and those with a BMI of 21-22 (RR-1.072, CI=95%: 0.759-1.514) compared with BMI between 23 -26.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>However relationship disappeared after excluding people who developed dementia early in the study.</td>
</tr>
<tr>
<td>(Ogunniyi et al., 2011)</td>
<td>1559</td>
<td>≥65</td>
<td>5.97</td>
<td>BMI</td>
<td>CERAD, Clinician Home-based Interview, and Cambridge Examination for Mental Disorders</td>
<td>A significantly greater decline in BMI was found in those with either incident dementia (p &lt; 0.001) or incident MCI (p &lt; 0.001) compared to healthy subjects.</td>
</tr>
<tr>
<td>(Power et al., 2011)</td>
<td>12,047</td>
<td>65-84 (mean 72.1)</td>
<td>9.7</td>
<td>BMI, WC, WHR</td>
<td>ICD-9 &amp; ICD-10 dx codes in Western Australia Data Linkage System</td>
<td>Overweight men and those with WHR ≥ 0.9 have lower risk of dementia than men with normal weight and with WHR &lt; 0.9. Higher adiposity was not associated with incident dementia.</td>
</tr>
</tbody>
</table>
### Table 1.3.3. Longitudinal studies not supporting an association between overweight and dementia.

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>Dementia Assessment</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Raffaitin et al., 2009)</td>
<td>2049</td>
<td>74</td>
<td>4</td>
<td>WC</td>
<td>MMSE, Benton Visual Retention Test, Isaac’s Set Test Dx VaD, AD</td>
<td>Participants with high WC had decreased risk for all-cause dementia (HR = 0.86, 95% CI: 0.64–1.17), AD (HR=0.63, 95% CI: 0.43–0.94) and VaD (HR=0.82, 95% CI: 0.41–1.66)</td>
</tr>
<tr>
<td>(West &amp; Haan, 2009)</td>
<td>1,351</td>
<td>60-101 (mean 69.9)</td>
<td>8 (5.6)</td>
<td>BMI, WC</td>
<td>3MSE and DelRec dx dementia by DSM-III</td>
<td>Compared with the lowest BMI category, overweight participants had a 48% decreased rate of dementia or being cognitively impaired not dementia (CIND) (adj [HR] = 0.52, 95% [CI]: 0.30-0.91) and obese participants had a 61% decreased rate of dementia/CIND (HR = 0.39, 95% CI: 0.20-0.78). By contrast, the middle and high tertiles of WC were associated with higher rates of dementia/CIND compared with the low tertile, (adj HR = 1.8, 95% CI: 1.1-3.1, and adj HR = 1.9, 95% CI: 0.91-3.8 respectively).</td>
</tr>
<tr>
<td>(Xiong, Plassman, Helms, &amp; Steffens, 2006)</td>
<td>166</td>
<td>65.81</td>
<td>12</td>
<td>BMI</td>
<td>Dementia dx: TICS-m and clinical assessments</td>
<td>Cognitive change was not significantly different between twins discordant for BMI.</td>
</tr>
</tbody>
</table>
Articles Assessing Mild Cognitive Impairment

Among the 5 longitudinal studies in which MCI was the principle cognitive outcome, none reported evidence supporting an association between obesity and increased risk MCI. In contrast, all 5 reported no association between obesity and MCI. Furthermore, all 5 studies (100%) were assessed among older adults, not midlife. Results are displayed in Table 1.3.4 below.
Table 1.3.4. Longitudinal studies not supporting an association between overweight and MCI.

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>MCI Assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Gao et al., 2011)</td>
<td>1331</td>
<td>≥65 mean 75.8</td>
<td>6.4 mean</td>
<td>BMI</td>
<td>CERAD, Clinician Home-based Interview, and Cambridge Examination for Mental Disorders</td>
<td>BMI in participants with incident MCI, did not differ 12 or 9 years before diagnosis, but 6 years before diagnosis, participants with incident MCI had significantly lower BMI than participants with normal cognition (p = .006). Participants with incident MCI had greater decline in BMI than those without (P = .04).</td>
</tr>
<tr>
<td>(Kerwin et al., 2011)</td>
<td>7163</td>
<td>65-80</td>
<td>4.4 mean</td>
<td>BMI, WHR</td>
<td>3MSE</td>
<td>Association between BMI and risk of CI was modified by body fat distribution (WHR). Older women with a lower WHR had greater risk of CI at both low and high BMI categories. Underweight women with a WHR less than 0.80 had a greater risk than those with higher BMI. In normal-weight to overweight women (BMI 20.0–29.9), central adiposity (WHR&gt;0.80) is associated with greater risk of cognitive impairment and probable dementia than in women with higher BMI.</td>
</tr>
<tr>
<td>(Newman et al., 2009)</td>
<td>1677</td>
<td>77-102 Median 85</td>
<td>13</td>
<td>WC, BMI</td>
<td>Modified MMSE, DSST, CES-D, CI based on &lt;80 on 3MS</td>
<td>Greater weight was not associated with higher rates of cognitive impairment. There was no significant association between WC and cognitive impairment.</td>
</tr>
<tr>
<td>(Ogunniyi et al., 2011)</td>
<td>1559</td>
<td>≥65</td>
<td>5.97 mean</td>
<td>BMI</td>
<td>CERAD, Clinician Home-based Interview, Cambridge Examination for Mental Disorders</td>
<td>A significantly greater decline in BMI was found in those later diagnosed with MCI (p &lt; 0.001) compared to normal subjects.</td>
</tr>
</tbody>
</table>
Longitudinal studies not supporting an association between overweight and MCI.

### Table 1.3.4

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>MCI Assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Sachs-Ericsson, Sawyer, Corsentino, Collins, &amp; Blazer, 2010)</td>
<td>2840</td>
<td>71.1(5.3)</td>
<td>4 times over 10 years</td>
<td>BMI</td>
<td>SPMSQ</td>
<td>Lower BMI was a predictor of CI for those with the APOE-ε4 allele. For non-APOE 4 allele carriers, BMI was unrelated to CI.</td>
</tr>
</tbody>
</table>
**Articles Assessing Cognitive Function**

Among the 26 articles assessing cognitive function outcomes other than MCI or dementia, one article reported both evidence that could be used to support and evidence that could be used to oppose an association (Kanaya et al., 2009), so that in total 14 studies were included in the table supporting an association between obesity and dementia, while 13 articles were included in the table opposing this association. The articles assessing the association between weight or adiposity and cognitive function tested a variety of cognitive domains, including memory, executive function, and attention, which are recorded in Table 1.3.5 and Table 1.3.6 below.

**Supporting an association between obesity and cognitive function:** Fourteen longitudinal studies reported evidence for an association between obesity and declines in various cognitive functions. Of these, 10 (71%) found that obesity in midlife increased risk of cognitive decline, while 4 (29%) reported that obesity in older adults increased risk of cognitive decline. Of the studies supporting a link, all 14 used BMI as an estimate of adiposity, only 4 combined BMI with waist circumference or waist-hip ratio (WHR).

**Opposing an association between obesity and cognitive function:** Thirteen longitudinal studies reported no evidence of an association between any measure of adiposity and cognitive decline. Four (31%) of these studies examined adiposity in midlife and 9 (69%) were among older adults. Among the studies not supporting an association, 11 used BMI to estimate obesity, while six used BMI combined with other measures such as WHR.
Table 1.3.5. Longitudinal studies supporting an association between overweight and cognitive decline.

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Measures</th>
<th>Cognitive Measures</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Albanese et al., 2012)</td>
<td>2083</td>
<td>Began at 15, 20, 26, 36, 43, and 53 years;</td>
<td>38</td>
<td>BMI</td>
<td>Animal naming, National Adult Reading Test, word list recall, letter cancellation</td>
<td>Midlife BMI gain from youth was inversely associated with memory in midlife. BMI gain from youth to age 53 years in men was independently associated with better memory. Average BMI was approx. 27 at age 53. Both underweight and obese women at 53 years had significantly lower memory scores, cross-sectionally.</td>
</tr>
<tr>
<td>(Cournot et al., 2006a)</td>
<td>2223</td>
<td>32-62</td>
<td>5</td>
<td>BMI</td>
<td>Word-list learning, Digit-Symbol Substitution Test, WAIS, selective attention test, delayed free recall test</td>
<td>Cross-sectionally, BMI was associated with lower cognitive scores. A higher BMI at baseline was also associated with a higher decline in word list learning (delayed recall) at follow-up. No significant association was found between changes in BMI and cognitive function.</td>
</tr>
<tr>
<td>(Dahl et al., 2010)</td>
<td>781</td>
<td>25-63 (mean 41.6)</td>
<td>16</td>
<td>BMI</td>
<td>Information Synonyms, Analogies, Figure Logic, Kohs Block Design, Card Rotations, Digit Span (Forward and Backward), Thurstone’s Picture Memory, Names and Faces, (Immediate and Delayed), Digit Symbol, Figure Identification</td>
<td>Higher midlife BMI scores preceded lower general cognitive ability and steeper cognitive decline in both men and women.</td>
</tr>
<tr>
<td>(Dahl et al., 2012)</td>
<td>657</td>
<td>≤50 (mean 39.9)</td>
<td>25</td>
<td>BMI</td>
<td>Test battery representing four domains: verbal, spatial/fluid, memory, and perceptual speed</td>
<td>Being overweight or obese in midlife was associated with cognitive decline later in life. Weight decline across midlife rather than low weight in late midlife per se was associated with cognitive decline.</td>
</tr>
</tbody>
</table>
### Table 1.3.5. Longitudinal studies supporting an association between overweight and cognitive decline.

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Measures</th>
<th>Cognitive Measures</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Debette et al., 2011)</td>
<td>1352</td>
<td>54 +/-9</td>
<td>6.3 +/-1.1</td>
<td>BMI, WHR</td>
<td>logical memory delayed recall, visual reproductions delayed-recall (VR-d), and Trail-Making Test B-A (TrB-A)</td>
<td>Midlife obesity was associated with an increased rate of progression of decline in executive function a decade later. Large WHR in midlife was associated with marked decline in total brain volume.</td>
</tr>
<tr>
<td>(Hassing, Dahl, Pedersen, &amp; Johansson, 2010)</td>
<td>417</td>
<td>50-60</td>
<td>30</td>
<td>BMI</td>
<td>long-term memory, short-term memory, speed, verbal and spatial ability</td>
<td>Midlife overweight is related to lower overall cognitive function in old age.</td>
</tr>
<tr>
<td>(Laitala et al., 2011)</td>
<td>2606 twins</td>
<td>Midlife</td>
<td>Old age</td>
<td>BMI</td>
<td>Validated telephone interview</td>
<td>Midlife overweight increased the risk for mild impairment of cognitive function. Weight gain more than 1.7 kg/m and loss more than 2 kg/m within an average of 5.6 years were associated with lower cognitive performance independently of BMI.</td>
</tr>
<tr>
<td>(Sabia, Kivimaki, Shipley, Marmot, &amp; Singh-Manoux, 2009)</td>
<td>10,308</td>
<td>35-55</td>
<td>21</td>
<td>BMI</td>
<td>MMSE, AH4-I, inductive reasoning, phonemic fluency</td>
<td>Long-term obesity and long-term underweight in adulthood are associated with lower cognitive scores in late midlife.</td>
</tr>
</tbody>
</table>
Longitudinal studies supporting an association between overweight and cognitive decline.

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Measures</th>
<th>Cognitive Measures</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Singh-Manoux et al., 2012)</td>
<td>6401</td>
<td>39-63 (mean 48.9-50.0)</td>
<td>10</td>
<td>BMI</td>
<td>Memory, reasoning, semantic, and phonemic fluency</td>
<td>In the metabolically abnormal group, the 10 year decline on the global cognitive score was faster among obese than among healthy weight individuals. In the metabolically normal group, the 10-year decline in the global cognitive score was similar in the normal weight, overweight, and obese groups.</td>
</tr>
<tr>
<td>(Wolf et al., 2007)</td>
<td>1814</td>
<td>40-69</td>
<td>8-12</td>
<td>BMI WHR</td>
<td>Trails B, Visual Reproductions-Immediate and Delayed Recall Verbal memory (immediate and delayed recall)</td>
<td>Midlife WHR in highest quartile was significantly related to poorer performance on executive function &amp; visuomotor skills. Obesity was not related to verbal memory (immediate or delayed recall). Visuomotor skills but not memory were related to WHR.</td>
</tr>
</tbody>
</table>
Table 1.3.5. Longitudinal studies supporting an association between overweight and cognitive decline.

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<th>Baseline Age</th>
<th>Follow-up (years)</th>
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<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Brubacher, Monsch, &amp; Stahelin, 2004)</td>
<td>531</td>
<td>59.4(7.9)</td>
<td>10</td>
<td>BMI</td>
<td>CERAD-NAB battery</td>
<td>This study demonstrates that for both BMI loss and BMI gain there is a worsening of cognition. Odds ratio is greater at the extremes of weight loss or weight gain, up to OR=4 for BMI loss of 0.8kg/m2/yr and up to OR = 8 for BMI gain of 0.8kg/m2/yr.</td>
</tr>
<tr>
<td>(Elias, Elias, Sullivan, Wolf, &amp; D'Agostino, 2003)</td>
<td>1423</td>
<td>55-88</td>
<td>18</td>
<td>BMI</td>
<td>Kaplan–Albert Neuropsychological Test Battery</td>
<td>Obese men performed at a level of 0.44 s.d. below the level of non-obese men for total test score (P&lt;0.0001). Obese vs. non-obese women showed no differences in total test score.</td>
</tr>
<tr>
<td>(Gunstad, Lhotsky, Wendell, Ferrucci, &amp; Zonderman, 2010)</td>
<td>1703</td>
<td>19-93 (Mean 55.5)</td>
<td>Average 3.1 visits, average 2.0 years between visits</td>
<td>BMI, WHR, WC</td>
<td>MMSE, BIMC, WAIS-R, CVLT, letter fluency, card rotation</td>
<td>Obesity was associated with poorer performance in a variety of cognitive domains, including global screening measures, memory, and verbal fluency tasks. Obesity was associated with better performance on tests of attention and visuospatial ability. An obesity by age interaction emerged in some domains, including memory, attention, executive function.</td>
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Table 1.3.5. Longitudinal studies supporting an association between overweight and cognitive decline.

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<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Kanaya et al., 2009)</td>
<td>3054</td>
<td>70-79</td>
<td>Up to 8</td>
<td>BMI, WC, sagittal diameter, total fat by DXA Subcutaneous and visceral fat by CT</td>
<td>3MS</td>
<td>In men higher levels of all adiposity measures were associated with worsening cognitive function in men. In women there was no association between adiposity and cognitive change.</td>
</tr>
</tbody>
</table>
### Table 1.3.6. Longitudinal studies not supporting an association between overweight and cognitive decline.

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Measures</th>
<th>Cognitive Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Arntzen, Schirmer, Wilsgaard, &amp; Mathiesen, 2011)</td>
<td>5033</td>
<td>59 mean</td>
<td>7</td>
<td>BMI</td>
<td>12 word memory, Digit-Symbol Coding, Tapping test</td>
<td>The authors found no consistent association between BMI and cognitive test results.</td>
</tr>
<tr>
<td>(Knopman, Mosley, Catellier, &amp; Coker, 2009)</td>
<td>1130</td>
<td>59.6 +/- 4.3</td>
<td>12-16?</td>
<td>BMI</td>
<td>Delayed Word Recall (DWR) Test, the Digit Symbol Substitution (DSS) Test, and the Word Fluency (WF) Test</td>
<td>Baseline BMI was not a risk factor for cognitive decline</td>
</tr>
<tr>
<td>(Lo, Pachana, Byrne, Sachdev, &amp; Woodman, 2012)</td>
<td>334</td>
<td>40-79 (Mean 58.72)</td>
<td>Mean 7.45</td>
<td>BMI, WC, WHR</td>
<td>MMSE, Auditory Delayed Index, Visual Delayed Index, and Working Memory Index from WMS. Processing Speed Index from WAIS.</td>
<td>No significant associations were found between BMI, WC, or WHR and any cognitive domains at follow-up. Both weight gain and loss were associated with poor Visual Delayed Index performance at follow-up compared with stable weight.</td>
</tr>
<tr>
<td>(Thilers, Macdonald, Nilsson, &amp; Herlitz, 2010)</td>
<td>1480</td>
<td>40-65</td>
<td>10</td>
<td>BMI</td>
<td>3MSE Spanish and English Verbal Learning Test (SEVLT)</td>
<td>Accelerated postmenopausal cognitive decline is restricted to women with normal BMI.</td>
</tr>
</tbody>
</table>
### Table 1.3.6: Longitudinal studies not supporting an association between overweight and cognitive decline.

<table>
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<tr>
<th>Author (date)</th>
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<tbody>
<tr>
<td>(Bagger, Tanko, Alexandersen, Qin, &amp; Christiansen, 2004)</td>
<td>5607</td>
<td>63.8</td>
<td>mean 7.3</td>
<td>Weight, DXA body composition, TFM, TLM, CFM</td>
<td>Short Blessed test</td>
<td>Higher baseline weight was associated with lower cognitive decline. Women with the worst cognitive performance at follow-up were the ones who lost the most body weight and had the lowest central fat mass (CFM).</td>
</tr>
<tr>
<td>(Deschamps et al., 2002)</td>
<td>169</td>
<td>69 to 89 Mean 75.4</td>
<td>5</td>
<td>BMI</td>
<td>ADL dependency, IADL dependency, MMSE</td>
<td>No overweight patients (BMI &gt;27) declined in cognitive function. Subjects with a BMI 23-27 had 3.6 times lower chance cognitive decline in the subsequent 5 y (OR=0.28, 95%, CI 0.09-0.90) than subjects with BMI less than 23.</td>
</tr>
<tr>
<td>(Driscoll et al., 2011)</td>
<td>2283</td>
<td>65-79 Mean 75.4</td>
<td>Up to 5 Mean 3</td>
<td>BMI, WHR, WC</td>
<td>3MS, PMA, Letter fluency, BVRT, CVLT, digital span, CRT,</td>
<td>No association between weight and cognition in women who remained stable or gained weight. Cognition was not related to changes in WC. Weight loss was associated with cognitive decline, independent of initial BMI.</td>
</tr>
<tr>
<td>(Han et al., 2009)</td>
<td>721</td>
<td>60-85</td>
<td>2.13</td>
<td>BMI, WHR, WC, and % body fat</td>
<td>CERAD-Korean version</td>
<td>For men obese at baseline, increasing adiposity (BMI, WHR, WC) was associated with improved cognitive function. For women obese at baseline, both an increase or decrease in WHR or WC were associated with cognitive decline.</td>
</tr>
<tr>
<td>(Kanaya et al., 2009)</td>
<td>3054</td>
<td>70-79</td>
<td>Up to 8</td>
<td>BMI, WC, sagittal diameter, total fat by DXA Subcutaneous and visceral fat by CT</td>
<td>3MS</td>
<td>There was no association between adiposity and cognitive change in women. Higher levels of all adiposity measures were associated with worsening cognitive function in men.</td>
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Table 1.3.6. Longitudinal studies not supporting an association between overweight and cognitive decline.

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<th>Author (date)</th>
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<th>Cognitive Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Raffaitin et al., 2011)</td>
<td>7087</td>
<td>65+</td>
<td>4</td>
<td>WC</td>
<td>MMSE, Isaacs Set Test (verbal fluency), Benton Visual Retention Test (BVRT, visual working memory)</td>
<td>No significant change in cognition in those who started with a high WC.</td>
</tr>
<tr>
<td>(Regal &amp; Heatherington, 2012)</td>
<td>94</td>
<td>71-86</td>
<td>1</td>
<td>BMI</td>
<td>MMSE, Montreal Cognitive Assessment, Frontal Assessment Battery, and Addenbrooke Cognitive Assessment</td>
<td>Underweight group had the lowest cognitive scores of the four groups in all 12 comparisons. The overweight group had the highest cognitive scores in nine of 12 comparisons.</td>
</tr>
<tr>
<td>(Sturman et al., 2008)</td>
<td>3885</td>
<td>65+</td>
<td>Up to 10 Mean 6.4</td>
<td>BMI</td>
<td>MMSE, East Boston Tests of Immediate Memory and Delayed Recall and the Symbol Digit Modalities Test</td>
<td>Among older adults, higher BMI was not predictive of cognitive decline.</td>
</tr>
<tr>
<td>(Xiong et al., 2006)</td>
<td>166 pairs of twins discordant for BMI</td>
<td>67-77</td>
<td>12</td>
<td>BMI &gt;30 kg/m</td>
<td>Modified Telephone Interview for Cognitive Status (TICS-m)</td>
<td>Cognitive change was not significantly different between members of pairs discordant for BMI.</td>
</tr>
</tbody>
</table>
Articles Measuring Central Obesity

Looking across the different studies examining cognitive function, MCI or dementia diagnosis outcomes, a total of 22 studies investigated the association between central obesity and any of these cognitive health outcomes. The results of these studies can be seen in Table 1.3.7 and Table 1.3.8.

Supporting an association between central obesity and cognitive health: A total of 11 studies reported an association between central obesity and cognitive outcomes. Six (55%) of these studies measured central obesity in midlife, while 5 (45%) measured central obesity in older adults.

Opposing an association between central obesity and cognitive health: In contrast, 12 studies reported no association between central obesity and cognitive outcomes. Only two (17%) of these studies reported the association with midlife central obesity, while 10 (83%) measured central obesity in older adults.

1.3.4 Conclusions

The existing empirical literature on weight and cognitive function reveals a mixture of results that support an association between increased weight and cognitive decline or dementia, and studies that do not. Among the studies that do not support this association, many report that low weight or weight loss increases risk. Some others report that higher weight may even be protective, decreasing risk of dementia or cognitive decline. However overall, it would appear that the mixed findings are at least partly due to differences between midlife and late life measures of adiposity. The majority of negative findings measured baseline adiposity among older adults (≥65 years), while the majority of positive findings were measured adiposity among adults in midlife. Research has indicated that weight loss is a common feature of dementia, and may precede dementia diagnosis by 6 years or more (Gao et al., 2011). It is therefore possible
that the baseline weight among older adults already reflected some of these changes. Upon comparison of the studies of older adult weight that were for or against the association there did not appear to be a systematic difference in follow-up time, but there may be other systematic differences not accounted for in this study.
Table 1.3.7. Longitudinal studies measuring central obesity that supported an association with any cognitive outcomes.

<table>
<thead>
<tr>
<th>STUDIES OF MIDLIFE CENTRAL ADIPOSITY</th>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>Dementia Assessment</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Beydoun &amp; Beason-Held, 2008)</td>
<td>2,322</td>
<td>≥20</td>
<td>23.4 years</td>
<td>BMI, WC</td>
<td>Dx AD, NINCDS-ADRDA criteria</td>
<td>Among men, being underweight (BMI &lt;or=18.5) at age 30, 40, or 45 years increased the likelihood of AD (HR = 5.76, 95% CI: 2.07, 16.00); among women, being obese (BMI &gt;/=30) at age 30, 40, or 45 years and jointly centrally obese (waist circumference &gt;/= 80th percentile) at age 30, 35, or 50 years increased AD risk (HR = 6.57, 95% CI: 1.96, 22.02). Women who lost weight (BMI change &lt;10th percentile) between ages 30 and 45 years were also at increased risk (HR = 2.02, 95% CI: 1.06, 3.85). Weight gain among men (BMI change &gt;90th percentile) between age 30 and 50 years increased AD risk (HR = 3.70, 95% CI: 1.43, 9.56).</td>
<td></td>
</tr>
<tr>
<td>(Debette et al., 2011)</td>
<td>1352</td>
<td>54 +/-9</td>
<td>6.3 +/-1.1</td>
<td>BMI, WHR</td>
<td>logical memory delayed recall, visual reproductions delayed-recall (VR-d), and Trail-Making Test B-A (TrB-A)</td>
<td>Midlife obesity was associated with an increased rate of progression of decline in executive function a decade later. Large WHR in midlife was associated with marked decline in total brain volume.</td>
<td></td>
</tr>
<tr>
<td>(Gustafson et al., 2009)</td>
<td>1462</td>
<td>38-60</td>
<td>32</td>
<td>BMI, WC, WHR</td>
<td>Dementia dx: DSM-III-R criteria; AD dx: NINCDS-ADRDA criteria; VaD dx: NINDS-AIREN criteria</td>
<td>While Cox models showed no association between baseline anthropometric factors and dementia risk, logistic models showed that a midlife WHR greater than 0.80 increased risk for dementia approximately twofold (odds ratio 2.22, 95% confidence interval 1.00–4.94, p=0.049) among surviving participants.</td>
<td></td>
</tr>
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Table 1.3.7. Longitudinal studies measuring central obesity that supported an association with any cognitive outcomes.

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<th>Dementia Assessment</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Whitmer et al., 2005)</td>
<td>10,276</td>
<td>40- 45</td>
<td>21-39</td>
<td>BMI, skinfold thickness</td>
<td>Dementia dx: ICD-9 codes</td>
<td>Compared with healthy weight:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Obesity in midlife (BMI &gt;= 30) increased risk of dementia 74% (HR 1.74, 95% CI 1.34 to 2.26).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Overweight in midlife (BMI 25.0-29.9) increased risk of dementia 35% (1.35, 1.14 to 1.60).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The highest quintile of skinfold thickness had a 72% greater risk of dementia than the lowest quintile (1.72, 1.36 to 2.18, and 1.59, 1.24 to 2.04).</td>
</tr>
<tr>
<td>(Whitmer et al., 2008)</td>
<td>6583</td>
<td>40-45</td>
<td>~26-42</td>
<td>BMI, Sagittal Abdominal Diameter (SAD)</td>
<td>ICD-9 codes</td>
<td>Persons in the highest quintile of SAD in midlife had increased risk of dementia (HR, 2.72; 95% CI, 2.33-3.33) compared to persons in the lowest quintile.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Those with high SAD (&gt;25 cm) but healthy BMI had an increased risk (HR, 1.89; 95% CI, 0.98-3.81) vs. those with low SAD (&lt;25 cm) and healthy BMI.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Persons who were both obese and with high SAD had the highest risk of dementia (HR, 3.60; 95% CI, 2.85-4.55).</td>
</tr>
<tr>
<td>(Wolf et al., 2007)</td>
<td>1814</td>
<td>40-69</td>
<td>8-12</td>
<td>BMI WHR</td>
<td>Trails B, Visual Reproductions-Immediate and Delayed Recall, Verbal memory (immediate and delayed recall)</td>
<td>Midlife WHR in highest quartile was significantly related to poorer performance on executive function &amp; visuomotor skills. Obesity was not related to verbal memory (immediate or delayed recall). Visuomotor skills but not memory were related to WHR.</td>
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Table 1.3.7. Longitudinal studies measuring central obesity that supported an association with any cognitive outcomes.

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<th>Author (date)</th>
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<th>Baseline Age</th>
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<td>(Gunstad et al., 2010)</td>
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<td>19-93 (Mean 55.5)</td>
<td>Average 3.1 visits,</td>
<td>BMI, WHR, WC</td>
<td>MMSE, BIMC, WAIS-R, CVLT, letter fluency, card rotation</td>
<td>Obesity was associated with poorer performance in a variety of cognitive domains, including global screening measures, memory, and verbal fluency tasks. Obesity was associated with better performance on tests of attention and visuospatial ability. An obesity by age interaction emerged in some domains, including memory, attention, executive function.</td>
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<td>(Kanaya et al., 2009)</td>
<td>3054</td>
<td>70-79</td>
<td>Up to 8</td>
<td>BMI, WC, sagittal diameter, total fat by DXA Subcutaneous and visceral fat by CT</td>
<td>3MS</td>
<td>In men higher levels of all adiposity measures were associated with worsening cognitive function in men. In women there was no association between adiposity and cognitive change.</td>
</tr>
<tr>
<td>(Kerwin et al., 2011)</td>
<td>7163</td>
<td>65 to 80</td>
<td>up to 8 average 4.4</td>
<td>WHR, BMI</td>
<td>3MSE Dementia Dx</td>
<td>Central obesity was what mattered. Women with a WHR of ≥0.80 and a BMI of 20.0 - 24.9 had a greater risk of cognitive impairment and probable dementia than more-obese women or women with a WHR less than 0.80. However women with a WHR less than 0.80 and a BMI of 20.0 to 24.9 kg/m2 had poorer scores on cognitive assessments.</td>
</tr>
</tbody>
</table>
Table 1.3.7. Longitudinal studies measuring central obesity that supported an association with any cognitive outcomes.

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<tr>
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<tr>
<td><strong>Author (date)</strong></td>
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<tr>
<td>(Luchsinger et al., 2007)</td>
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<td>(Luchsinger et al., 2012)</td>
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</table>
Table 1.3.8. Longitudinal studies measuring central obesity that did not support a link between obesity and cognitive outcomes.

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<th>Author (date)</th>
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<tbody>
<tr>
<td>(Lo et al., 2012)</td>
<td>334</td>
<td>40-79 (Mean 58.72)</td>
<td>Mean 7.45</td>
<td>Weight, WC, WHR</td>
<td>MMSE, Auditory Delayed Index, Visual Delayed Index, and Working Memory Index from WMS, Processing Speed Index from WAIS</td>
<td>No significant associations were found between BMI, WC, or WHR and any cognitive domains at follow-up. Both weight gain and loss were associated with poor Visual Delayed Index performance at follow-up compared with stable weight.</td>
</tr>
<tr>
<td>(Newman et al., 2009)</td>
<td>1677</td>
<td>77-102 Median 85</td>
<td>13</td>
<td>WC, BMI</td>
<td>Modified MMSE, DSST, CES-D, CI based on &lt;80 on 3MS</td>
<td>Greater weight was not associated with higher rates of cognitive impairment. There was no significant association between WC and cognitive impairment.</td>
</tr>
</tbody>
</table>
### Table 1.3.8. Longitudinal studies measuring central obesity that did not support a link between obesity and cognitive outcomes.

#### STUDIES OF CENTRAL ADIPOSEITY IN OLDER ADULTS

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<td>(Bagger et al., 2004)</td>
<td>5607</td>
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<td>mean 7.3</td>
<td>Weight, DXA body composition, TFM, TLM, CFM</td>
<td>Short Blessed test</td>
<td>Higher baseline weight was associated with lower cognitive decline. Women with the worst cognitive performance at follow-up were the ones who lost the most body weight and had the lowest central fat mass (CFM).</td>
</tr>
<tr>
<td>(Driscoll et al., 2011)</td>
<td>2283</td>
<td>65-79</td>
<td>Up to 5 Mean 3</td>
<td>BMI, WHR, WC</td>
<td>3MS, PMA, Letter fluency, BVRT, CVLT, digital span, CRT,</td>
<td>No association between weight and cognition in women who remained stable or gained weight. Cognition was not related to changes in WC. Weight loss was associated with cognitive decline, independent of initial BMI.</td>
</tr>
<tr>
<td>(Forti et al., 2010)</td>
<td>749</td>
<td>≥65</td>
<td>3-5</td>
<td>Metabolic Syndrome (MetS) WC</td>
<td>MMSE DxD VaD, AD</td>
<td>In participants aged 75 and older, abdominal obesity was associated with a lower risk of overall dementia (HR = 0.53, 95% CI = 0.28-0.98).</td>
</tr>
<tr>
<td>(Han et al., 2009)</td>
<td>721</td>
<td>60-85</td>
<td>2</td>
<td>BMI, WHR, WC, PBF</td>
<td>CERAD-Korean version Dementia dx using DSM-IV criteria</td>
<td>For men obese at baseline, increasing adiposity (BMI, WHR, WC) was associated with improved cognitive function. For women obese at baseline, both an increase or decrease in WHR or WC were associated with cognitive decline</td>
</tr>
<tr>
<td>(Hughes et al., 2009)</td>
<td>1,478</td>
<td>Japanese Americans of the Kame Project</td>
<td>mean age of 71.8 years and were dementia-free at baseline (1992-1994)</td>
<td>Biennially for 8 years (mean 7.8)</td>
<td>BMI, WC, WHR</td>
<td>Cognitive Abilities Screening Instrument and CERAD dx using DSM-IV criteria</td>
</tr>
</tbody>
</table>
Table 1.3.8. Longitudinal studies measuring central obesity that did not support a link between obesity and cognitive outcomes.

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N</th>
<th>Baseline Age</th>
<th>Follow-up (years)</th>
<th>Weight Assessment</th>
<th>Dementia Assessment</th>
<th>Risk ratio Hazard ratio, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Kanaya et al., 2009)</td>
<td>3054</td>
<td>70-79</td>
<td>Up to 8</td>
<td>BMI, WC, sagittal diameter, total fat by DXA Subcutaneous and visceral fat by CT</td>
<td>3MS</td>
<td>There was no association between adiposity and cognitive change in women. Higher levels of all adiposity measures were associated with worsening cognitive function in men.</td>
</tr>
<tr>
<td>(Power et al., 2011)</td>
<td>12,047</td>
<td>65-84 (mean 72.1)</td>
<td>9.7</td>
<td>BMI, WC, WHR</td>
<td>ICD-9 &amp; ICD-10 dx codes in Western Australia Data Linkage System</td>
<td>Overweight men and those with WHR ≥ 0.9 have lower risk of dementia than men with normal weight and with WHR &lt; 0.9. Higher adiposity was not associated with incident dementia.</td>
</tr>
<tr>
<td>(Raffaitin et al., 2009)</td>
<td>2049</td>
<td>74</td>
<td>4</td>
<td>WC</td>
<td>MMSE, Benton Visual Retention Test, Isaac’s Set Test Dx VaD, AD</td>
<td>Participants with high WC had decreased risk for all-cause dementia (HR = 0.86, 95% CI: 0.64–1.17), AD (HR=0.63, 95% CI: 0.43–0.94) and VaD (HR=0.82, 95% CI: 0.41–1.66)</td>
</tr>
<tr>
<td>(Raffaitin et al., 2011)</td>
<td>7087</td>
<td>65+</td>
<td>4</td>
<td>WC</td>
<td>MMSE, Isaacs Set Test (verbal fluency), Benton Visual Retention Test (BVRT, visual working memory)</td>
<td>No significant change in cognition in those who started with a high WC.</td>
</tr>
<tr>
<td>(West &amp; Haan, 2009)</td>
<td>1,351</td>
<td>60-101 (mean 69.9)</td>
<td>8 (5.6)</td>
<td>BMI and WC</td>
<td>3MSE and DelRec dx dementia by DSM-III</td>
<td>Compared with the lowest BMI category, overweight participants had a 48% decreased rate of dementia or being cognitively impaired not dementia (CIND) (adj HR = 0.52, 95% [CI]: 0.30-0.91) and obese participants had a 61% decreased rate of dementia/CIND (HR = 0.39, 95% CI: 0.20-0.78). By contrast, the middle and high tertiles of WC were associated with higher rates of dementia/CIND compared with the low tertile, (adj HR = 1.8, 95% CI: 1.1-3.1, and adj HR = 1.9, 95% CI: 0.91-3.8 respectively).</td>
</tr>
</tbody>
</table>
For risk of incident dementia, there appears to be an increased risk associated with midlife obesity. More studies assessed incident dementia than any other category. Among these studies, diagnosis of dementia was generally made along similar criteria, such as DSM-IV or NINCDS-ADRDA criteria. It is worth noting that many of these studies specifically examined the diagnosis of AD, as opposed to simply all-cause dementia, including 15 of the studies supporting an association between overweight and dementia. Therefore the obesity-dementia link is not restricted to VaD, although this too was apparent.

Relatively little research has been conducted on the association between adiposity and MCI. Importantly, no research studies have examined midlife adiposity in relation to incident MCI. This may explain why no studies supported an association between overweight and MCI. Clearly further research assessing midlife adiposity and incident MCI is needed. This may be particularly important because MCI often represents a prodromal, stage of dementia – one which is clinically identifiable yet early enough to be amenable to effective intervention. In any case, primary prevention of MCI may be just as valuable as (or equivalent to) prevention of dementia. Studies of incident dementia could add this to the available outcome measures to increase the useful information.

The current literature on cognitive function suggests that being overweight in midlife may increase risk of declines in a broad range of cognitive functions. Positive results were not restricted to memory, nor any other cognitive domain, though memory was certainly represented in both groups. Among studies of baseline adiposity in older adults, weight was related to cognitive function but it was more common to find an association between low weight and cognitive decline.

Despite these findings, the current literature on obesity and cognitive health is limited by its reliance on BMI as the principle measure of adiposity. The majority of studies relied on
BMI alone, without inclusion of measures of fat distribution. This may have been a particular problem for baseline weight among older adults, who tend to lose lean mass as they age, making BMI a poor reflection of adiposity. It is possible that the reliance on BMI has contributed to the mixed findings. To investigate whether central obesity is more closely associated with cognitive decline or dementia than BMI we examined the studies of central obesity separately. Across all categories of cognitive outcome the number of studies for and against an association were approximately equal. Evidence for an association included a roughly equal mix of studies using midlife vs. older adult adiposity measures at baseline. However the vast majority of negative studies (83%) were among older adults at baseline. Therefore central obesity among older adults did not seem to increase risk of cognitive decline or dementia. By contrast, central obesity in midlife tended to do so.

In conclusion, the evidence to date suggests that midlife adiposity, whether global or central, may increase risk of cognitive decline and dementia later in life. As this is drawn from observational studies there is clearly a need for further research to investigate whether adiposity plays a causal role, or whether the association is simply an artifact of other factors such as poor nutrition or sedentary lifestyle. Inclusion of potential mechanisms that could mediate an effect of obesity on neurocognitive health could add valuable information to our understanding here. In addition weight loss studies may be useful, but should be conducted with caution and appropriate safety measures given the evidence linking weight loss to increased risk of cognitive decline and dementia. A systematic investigation of the effects of weight loss on cognitive function is warranted before proceeding in this direction.

**Limitations of Current Research**

While the convenience of BMI makes it an understandable first choice measure of adiposity, the evidence linking obesity to cognitive health would be strengthened by the use of
more accurate measures of adiposity. This is particularly important among older adults, where BMI can be a poor reflection of body fat.

While many of these studies provide valuable information about real-world associations in community-dwelling adults, the observational study designs cannot be used to determine causality. Even among well-controlled longitudinal studies it remains possible that some other factor related to obesity is in fact responsible for the cognitive decline.

Most of the studies controlled for socio-demographic factors such as education or SES, and many controlled for related health conditions such as diabetes or cardiovascular risk factors, including smoking, but few controlled for health-related behaviors linked to obesity, such as quality of diet, physical activity, social support or stress. Furthermore, few studies of the association between weight or adiposity and cognitive health outcomes have directly measured mechanisms that could potentially mediate a link between obesity and risk of dementia. We therefore discuss some of the potential confounding factors and mediating mechanisms that could be implicated in an association between obesity and cognitive function.

1.4 Potential Confounding Factors

In the previous section we reported epidemiological evidence of a link between midlife obesity and cognitive decline or risk of dementia later in life. However it remains possible that the apparent link is due to other factors also related to obesity, rather than obesity per se. Many of the observational studies described above statistically adjusted for some of these factors, however none accounted for all of them. Such potential confounding factors could include education (Evans et al., 2003; Evans et al., 1997; Fitzpatrick et al., 2004; Kukull et al., 2002), depression (Green et al., 2003a), sleep apnea (Bédard, Montplaisir, Malo, Richer, & Rouleau, 1993; Grigg-Damberger & Ralls, 2012), physical inactivity (Plassman et al., 2010) and poor
nutrition (Solfrizzi, Panza, & Capurso, 2003). Reverse causation is also possible – the potential that cognitive impairment or neural damage precedes or even contributes to obesity. The following sections give an overview of evidence regarding these different factors.

1.4.1 Education

Lower levels of education are associated with increased risk of dementia, even after controlling for socio-economic status (Evans et al., 2003; Evans et al., 1997; Fitzpatrick et al., 2004; Kukull et al., 2002; Stern, 2002). The association is not simply for all-cause dementia, nor just VaD. For example Evans et al. (1997) calculated that the risk of AD was reduced by 17% for every additional year of educational attainment. In a meta-analysis of 10 studies available before 2005, Caamaño-Isorna, Corral, Montes-Martínez, and Takkouche (2006) found that compared to persons with high education level, persons with low education had a 59% increased risk of all dementias (95% CI: 1.26–2.01), with the risk of non-AD dementias was 1.32 (95% CI: 0.92–1.88), and the risk for AD of 1.80 (95% CI: 1.43–2.27). Similarly Meng and D’Arcy (2012) analyzed 133 articles with 437,477 subjects published before 2011 and found that low education increased risk of AD, VaD and unspecified dementia. The pooled incidence studies gave an odd ratio of 1.88 (95%CI 1.51–2.34). McDowell, Xi, Lindsay, and Tierney (2007), examined the compounding effect of socioeconomic and health factors associated with higher education and determined that these could reduce but not remove the association of higher education and lower risk of dementia.

The finding that lower education increases risk of dementia cannot yet be fully explained. According to one theory, education may build “cognitive reserve” that helps to delay the detection of cognitive decline (Stern, 2002, 2009). The cognitive reserve hypothesis is also used to explain how some people with pathological signs of AD plaques and tangles never develop symptoms within their lifetime (Roe, Xiong, Miller, & Morris, 2007). In an alternative
hypothesis for the link with education, it is possible that people with early cognitive deficits or early stages of AD pathology may be less inclined to seek out mental stimulation many years before dementia symptoms appear. It is also possible that people who have low education may share a common set of independent risk factors. Education might be associated with good lifestyle choices that reduce dementia risk, such as avoiding smoking, maintaining a healthy weight, or avoiding diabetes (Knopman, 2008).

The association between education and obesity is complex, likely confounded by many other factors. In addition, as overweight and obesity have become increasingly widespread across the population in recent decades, the association has likely changed. There may have been an increased risk of obesity with less educated individuals in the past, however more contemporary analyses have found that the differentials may vary by sex and race (Yu, 2013) found the majority of the differences between education and obesity disappeared after careful adjustments, and only white college graduates were found to be less obese than white high school graduates.

1.4.2 Sleep Apnea

Obstructive sleep apnea (OSA) is a disorder of sleep caused by frequent collapse of the pharyngeal airway during sleep causing airways obstruction (Rosenberg & Doghramji, 2009). It is usually diagnosed when the number of disordered breathing events per hour is ≥5 (Rosenberg & Doghramji, 2009). In the general population approximately 3-7% in men and 2-5% in women have OSA (Lurie, 2011). However prevalence rises significantly with increasing weight (Pillar & Shehadeh, 2008). Among obese patients who present for bariatric surgery incidence of OSA can be as high as 78% (Lopez, Stefan, Schulman, & Byers, 2008). Incidence also increases with age (Lam, Sharma, & Lam, 2010). Up to 20% of adults over 70 years of age have OSA (Onen & Onen, 2010). Ancoli-Israel, Klauber, Butters, Parker, and Kripke (1991) reported that in a sample of 235
nursing home patients with median age 83.5 (women) and 79.7 (men), 96% had some degree of dementia and 70% had symptoms of sleep apnea.

Obstructive sleep apnea can cause neurocognitive damage across the lifespan (Bédard et al., 1993; Grigg-Damberger & Ralls, 2012). It can also exacerbate cognitive dysfunction in the elderly (Cooke et al., 2009; Kim, Lee, Lee, Jhoo, & Woo, 2011). Studies of the effects of CPAP treatment for OSA on neurocognitive outcomes have produced mixed results (e.g. (Cooke et al., 2009); compare (Ancoli-Israel et al., 1991).

The association of OSA with cognitive impairment and AD in elderly patients does not answer the question of causation. This is an area of active research (Roth, 2012). However given the link between OSA and obesity it is a potential confounding factor that ought to be addressed in future studies of the effects of obesity and cognitive function where possible.

1.4.3 Depression

Depressive symptoms are often associated with the development of AD and may appear years before clinical AD diagnosis (Green et al., 2003b). However it is difficult to determine whether these symptoms represent early manifestations of dementia, or whether depression itself is a risk factor for AD. Major depression can lead to difficulty concentrating, memory impairment, and difficulty making decisions (Taylor Tavares et al., 2007), which are also features of AD (Sinz, Zamar, Benke, Wenning, & Delazer, 2008; Zamar, Sinz, Bonatti, Gamboz, & Delazer, 2008). Furthermore persons with a history of depression are 2.5 times more likely to develop AD than those who did not, and persons who experienced depression before age 60 have been found to be more than 4 times more likely to develop AD (Geerlings, Den Heijer, Koudstaal, Hofman, & Breteler, 2008). The nature of the association between depression and obesity is less clear. Depression and obesity often co-occur (Appelhans et al., 2012; Luppino et al., 2010; Zhao et al., 2011), however some studies find no association (Hach et al., 2007;
In a study of 2,439 adults from the NHANES data, (Zhao et al., 2011) demonstrated an incidence of major depressive symptoms in 1% of the general population vs. 3% in the obese group and an incidence of moderate to severe depressive symptoms as 2.4% in the general population and 6.7% in the obese group.

While the relationship between depression and obesity needs further clarification, potential depression should be accounted for in studies of neurocognitive health and dementia risk.

1.4.4 Poor Nutrition

It is also possible that persons who are overweight or obese in midlife have had poor nutritional intake over many years. Nutritional deficiencies, rather than adiposity, could be the cause for cognitive deficits. Over the past decade, a large number of studies have been conducted to investigate the association between dietary composition and risk of dementia, and this continues to be an active area of research.

Nutritional deficiencies can also cause impaired cognitive function more generally (Solfrizzi et al., 2003). Deficiencies in essential micro-nutrients such as antioxidants (Vitamins C, E, carotenes, etc.) and B vitamins have been associated with cognitive impairment (Del Parigi, Panza, Capurso, & Solfrizzi, 2006). In addition, in some cross-sectional studies higher intake of healthy foods was associated with better cognition, while intake of refined sugars, high cholesterol and trans fats were associated with poorer cognitive performance (Lee et al., 2001; Requejo et al., 2003). Higher intake of mono-unsaturated and polyunsaturated fatty acids has been linked to better cognitive function and lower rates of cognitive decline. (Morris et al., 2003; Solfrizzi et al., 2005; Solfrizzi et al., 2003).

There is also some evidence to suggest that nutritional factors could influence risk of dementia. From a whole food perspective, there is evidence that persons who adhere to the Mediterranean diet have lower risk of dementia (Scarmeas, Stern, Mayeux, & Luchsinger, 2006).
The strength of these findings was reflected in a recent NIH consensus report on preventing cognitive decline and dementia, which reported that the Mediterranean diet is associated with decreased risk of cognitive decline and dementia (Plassman et al., 2010). Observational studies also link anti-oxidants such as Vitamin E and C to reduced risk of dementia (Engelhart et al., 2002; Morris, 2005; Morris et al., 2002), however the NIH report found that there is currently insufficient evidence to determine if this is true. Overall, the NIH report (Plassman et al., 2010) concluded that the strength of evidence is currently insufficient to claim that specific nutrients decrease risk of dementia. Clearly there is much more work to be done in this area, however dietary composition should be considered in a thorough investigation of the association between obesity and neurocognitive health outcomes.

1.4.5 Physical Inactivity

Persons who are overweight or obese are also less likely to be physically active than the general population (Church et al., 2011; Tudor-Locke, Brashear, Johnson, & Katzmarzyk, 2010). If physical inactivity impacts risk of cognitive decline or dementia then the association between weight and dementia risk could be due to the adverse effects of physical activity, rather than to obesity per se.

There is a growing body of evidence supporting an important role for physical activity in promoting neural and cognitive health. Many observational studies report an association between physical activity and lower risk of cognitive decline or dementia (Middleton & Yaffe, 2009). A recent meta-analysis (Skog, date) of prospective cohort studies found that 10 of 11 studies reported reduced risk of cognitive decline or dementia among adults who regularly engaged in physical activity in midlife. While the epidemiological evidence is promising, the NIH consensus report on preventing cognitive decline and dementia, found that there is currently insufficient evidence from randomized controlled trials (RCTs) to conclude that physical activity
protects against cognitive decline and dementia (Plassman et al., 2010). Similarly Snowden and colleagues (Snowden et al., 2011) found that there was not enough available data from quality intervention studies to determine whether physical activity interventions improve cognitive function in older adults. Nonetheless, the association seen in observational studies and small clinical trials suggests that physical activity should be considered in assessments of the association between obesity and dementia.

1.4.6 Reverse Causation

It remains possible that poor cognitive function can contribute to the development of obesity, rather than the reverse. This would be consistent with the findings of Cournot et al (Cournot et al., 2006b) that obesity in midlife was associated with increased risk of cognitive decline later in life, but change in weight over time (including weight gain) was not associated with increased risk of cognitive decline. Halkjær, Holst, and Sørensen (2003) demonstrated that intelligence test score was inversely related to the risk of developing obesity in a longitudinal study of 1709 men (median age 19) over more than two decades.

Experimental studies are needed before the question of causation can be adequately addressed. Interventions that reduce midlife obesity and measure incident dementia in older age would be ideal. Such a study would be particularly difficult to implement given the large sample size and long follow-up periods required. Experimental studies of more short-term effects of weight loss on neurocognitive outcomes and on potential mechanisms implicated in AD pathology would be more immediately practicable. The short-term effects of weight loss interventions on adult neurocognitive health will be discussed in section 3.
1.5 Potential Mechanisms Linking Adiposity to Dementia Risk

1.5.1 Alzheimer’s Disease Pathophysiology: A Brief Overview

While the pathophysiology of AD is not yet fully understood, many useful advances have been made in this field in recent decades. The prevailing theory of AD pathophysiology holds that the β-amyloid-42 plaques which characterize the disease directly contribute to neuronal death, though the possibility that β-amyloid is instead a by-product of the real underlying problem cannot yet be ruled out (Budson & Solomon, 2011; Resende, Ferreiro, Pereira, & Oliveira, 2008). Beta-amyloid is produced from the Amyloid Precursor Protein (APP), and is found in the healthy human brain, though its function is not known. The reasons for β-amyloid accumulation are still under investigation. However some of the factors that could serve as physiological mechanisms mediating an effect of obesity on neurocognitive health have already been linked to increased β-amyloid burden (Craft, 2005; Zhao et al., 2003).

1.5.2 Insulin Resistance and Glucose Regulation

Glucose dysregulation is one factor which could mediate an effect of obesity on risk of AD. Impaired glucose regulation and insulin resistance are common features of obesity, and insulin resistance is a central feature of both the metabolic syndrome (MetS) and Type 2 diabetes mellitus (T2DM). As already noted, persons with T2DM, are at increased risk of cognitive decline or dementia, including AD (Biessels & Gispen, 2005; Elias et al., 2005; Yaffe et al., 2004a). However, non-diabetic individuals with insulin resistance also show some evidence of deficits in learning and memory (Vanhanen et al., 1997; Vanhanen et al., 2006), even after controlling for vascular factors (Convit et al., 2003). In animal studies, a dose-response relationship can be seen, with worse memory performance and smaller hippocampal volumes recorded for animals with worse glycemic control, independent of age and overall cognitive function (Convit et al., 2003).
Insulin resistance and hyperglycemia in the peripheral circulation can have significant effects on neural glucose availability and on insulin levels in the brain. Growing evidence indicates that peripheral insulin resistance and hyperglycemia can decrease the transport of glucose across the blood-brain barrier (BBB) (McNay, Fries, & Gold, 2000), resulting in hypoglycemia in the brain. Since neurons depend on glucose for energy the effect may be devastating, particularly for brain regions frequently activated. Peripheral insulin resistance and hyperinsulinemia also decrease insulin transport across the BBB, leading to insulin deficiency in the brain (Baura et al., 1996; Kaiyala, Prigeon, Kahn, Woods, & Schwartz, 2000). Insulin receptors can be found in particularly high concentrations in the hippocampus, a brain region involved in learning and memory (Bingham et al., 2002; Jacobson & Sapolsky, 1991). Insulin may affect memory through direct receptor-mediated effects (Craft, 2007).

Thus the brain of a person with peripheral insulin resistance, hyperglycemia and hyperinsulinemia may become hypoglycemic and lacking the insulin normally involved in memory function. Furthermore, raised serum insulin levels have been shown to increase β-amyloid formation in the brain and decrease its clearance to the periphery (Craft, 2005; Ho et al., 2004; Marambaud, Zhao, & Davies, 2005; Zhao, Tuominen, & Kinnunen, 2004). Consistent with these findings, patients with AD have high rates of glucose dysregulation (Craft, 2007) and post-mortem reveals decreased insulin in the brains of AD patients relative to controls (Cole & Frautschy, 2007; Rivera et al., 2005; Steen et al., 2005).

1.5.3 Hypertension

Hypertension is normally defined as a systolic blood pressure of 140mmHg or higher or a diastolic pressure of 90mmHg or higher (Carretero & Oparil, 2000). In the general population, prevalence of hypertension in adults is estimated at 24% in the USA (Burt et al., 1995), and 26% worldwide (Kearney et al., 2005). Reviews indicate that those who are obese are more likely
than non-obese individuals to be hypertensive (Koebnick et al., 2012; McAuley et al., 2012; McAuley et al., 2009). There are several potential reasons for this. Persons who are obese tend to have higher levels of insulin and insulin stimulates the sympathetic nervous system, stimulating the kidneys to retain sodium (Krieger & Landsberg, 1988). Obesity also increases leptin levels, and leptin has been shown to increase blood pressure (Landsberg, 2001). Obesity can also contribute to increased aldosterone production (Ahmed, Fisher, Stevanovic, & Hollenberg, 2005; Sarzani, Salvi, Dessi-Fulgheri, & Rappelli, 2008) and is associated with a high incidence of obstructive sleep apnoea (Gami et al., 2004), which can increase sympathetic nervous system output.

Hypertension has been linked to increased risk of MCI (Reitz et al., 2010) and dementia (Kivipelto et al., 2001; Launer et al., 2000). For example, Kivipelto et al. (2001) found that people with raised systolic blood pressure (SBP) (≥160 mm Hg) in midlife had a more than two-fold higher risk of AD in later life, compared to persons with normal SBP (OR 2.3, 95% CI: 1.0 - 5.5). In this study diastolic blood pressure (DBP) in midlife had no significant effect on the risk of AD. In contrast Launer et al. (2000) found an association for both SBP and DBP in midlife with incident dementia. Incidence of dementia among men with hypertension in midlife whose hypertension was never treated increased almost five-fold in those with SBP 160 mm Hg and higher compared with SBP of 110 to 139 mm Hg (OR 4.8, 95% CI: 2.0-11.0). Risk of dementia was also increased for DBP of 90-94 mm Hg (OR 3.8, 95% CI: 1.6-8.7), and for DBP of 95 mmHg and over (OR 4.3, 95% CI: 1.7-10.8), compared to those with DBP of 80 to 89 mm Hg. By contrast, men whose hypertension was treated showed no increased risk for dementia. Consistent with this, Forette et al. (1998) demonstrated that lowering of SBP in elderly patients significantly reduced the incidence of dementia. At a structural level, Petrovitch et al. (2000) showed that midlife
hypertension was associated with neurofibrillary tangles (for DBP ≥ 95 mm Hg), amyloid plaques and low brain weight at autopsy (for SBP ≥ 160 mm Hg).

In contrast to these studies of midlife hypertension increases risk, some studies have indicated that hypotension late in life is associated with increased dementia risk. For example Guo, Viitanen, Fratiglioni, and Winblad (1996) noted that people with moderate or severe dementia were more likely persons without dementia to have hypotension, either systolic or diastolic. Similarly Qiu, Winblad, and Fratiglioni (2009) found low blood pressure to be associated with a more than two-fold increased risk of dementia or AD specifically, and Morris et al. (2000) showed the same relationship with AD.

These findings may point to a non-linear, inverse U-shaped relationship between blood pressure and cognitive health. In support of this, Razay, Williams, King, Smith, and Wilcock (2009) found that among persons with AD rate of cognitive decline was increased in the groups with either high or low DBP. Glynn et al. (1999) found a similar U shaped relationship with both diastolic blood pressure and systolic blood pressure. As with the studies described above, their results also suggest that midlife hypertension is a stronger risk factor for dementia than hypertension later in life.

1.5.4 Dyslipidemia

Dyslipidemia, or abnormally elevated lipids in the bloodstream, is another common feature of obesity (Nguyen, Magno, Lane, Hinojosa, & Lane, 2008). Dyslipidemia has been associated with increased risk of dementia. High total cholesterol in midlife has been associated with an increased risk for AD (Anstey, Lipnicki, & Low, 2008; Kivipelto et al., 2002; Solomon et al., 2007b). By contrast, high total cholesterol late in life was not associated with MCI (Reitz et al., 2008) nor with dementia (Anstey et al., 2008; Reitz, Luchsinger, Tang, Manly, & Mayeux, 2005; Solomon et al., 2007a). However neither high total cholesterol nor high triglycerides late in life
were associated with reduced risk of dementia (Mielke et al., 2005). Interestingly, Solomon et al. (2007a) noted that a moderate fall in TC levels between midlife and late-life was associated with a more severe cognitive impairment.

As with other intervention trials for symptomatic dementia, various studies report that use of statins in treatment of persons with established AD did not produce improvements in symptoms (Feldman et al., 2010; McGuinness et al., 2010; Sano et al., 2011) nor did they produce improvements in subjects who were 65 years of age or older (Arvanitakis et al., 2008; Rea et al., 2005; Zandi et al., 2005). By contrast other studies examining the potential for statins to prevent dementia have demonstrated a positive association (Cramer, Haan, Galea, Langa, & Kalbfleisch, 2008; Haag, Hofman, Koudstaal, Stricker, & Breteler, 2009; Jick, Zornberg, Jick, Seshadri, & Drachman, 2000; Wolozin, Kellman, Ruosseau, Celesia, & Siegel, 2000; Wolozin et al., 2007), though the NIH consensus report on preventing cognitive decline and dementia found that there is no consistent association and still insufficient evidence to claim that statin use reduces risk of dementia (Plassman et al., 2010).

1.5.5 Oxidative Stress

Cellular damage by free radicals, such as reactive oxygen species, may be a universal feature of the aging process (Calabrese et al., 2010; Knight, 2000; Nunomura et al., 2012). Affecting proteins, lipids and nucleic acids this oxidative damage, or oxidative stress, is normally met by anti-oxidant defenses (Texel & Mattson, 2011). When these defenses are inadequate, overwhelmed or exhausted tissue damage occurs (Friguet, 2002; Squier, 2001; Venkateshappa, Harish, Mahadevan, Srinivas Bharath, & Shankar, 2012). The role of oxidative stress in AD continues to be investigated as it may provide a trigger for some of the initial neural damage (Foley & White, 2002; Sultana & Butterfield, 2008).
1.5.6 Leptin and Leptin Resistance

Leptin is a hormone secreted by adipocytes, Leptin levels are proportional to adiposity in normal individuals (Ingvartsen & Boisclair, 2001; Popovic & Duntas, 2005). Although obese individuals often have high leptin levels, many lack a normal response to leptin administration, suggesting leptin resistance (Jung and Kim, 2013). This may occur for a variety of reasons, including defective signaling pathways (Sahu, 2003), fructose consumption (Scarpace & Zhang, 2009; Shapiro et al., 2008; Shapiro, Tümner, Gao, Cheng, & Scarpace, 2011), high sucrose and fat diets (Vasselli, Scarpace, Harris, & Banks, 2013) or as a response to hyperleptinemia (Knight, Hannan, Greenberg, & Friedman, 2010).

Leptin’s actions include regulation of appetite, stimulation of thermogenesis, enhancement of fatty acid oxidation, decreasing glucose, and reduction of body weight and fat (Yadav, Kataria, Saini, & Yadav, 2012). Consistent with its regulatory roles, leptin receptors can be found in the cerebral cortex, cerebellum, brainstem, basal ganglia, and hippocampus (Harvey, 2003). Leptin also has effects on immunity (Ingvartsen & Boisclair, 2001). Leptin deficiency is rare, but leads to severe obesity, hyperphagia, hypogonadism, hyperinsulinemia, hypercholesterolemia and impaired immune function, all of which reverse with leptin administration (Farooqi & O’Rahilly, 2009).

Leptin appears to have additional effects on the brain beyond the regulation of appetite or weight. In particular, it has been implicated in AD pathology and symptoms. Leptin has been shown to reduce β-amyloid levels in vitro and brain levels of β-amyloid in vivo (Fewlass et al., 2004). Levels have been shown to be decreased in AD, with serum levels inversely proportional to AD severity (Greco, Sarkar, Johnston, & Tezapsidis, 2009; Holden et al., 2009). In a study of 2,871 older adults, Holden and colleagues (2009), followed over a period of four years, demonstrated that those with a higher initial leptin level had lower rates of cognitive decline,
independent of other comorbidities or body fat (OR=0.66 95% CI: 0.48-0.91). Interestingly, Zeki Al Hazzouri and colleagues (Zeki Al Hazzouri, Haan, Whitmer, Yaffe, & Neuhaus, 2012) demonstrated that a raised leptin level in elderly women of normal weight - but not in overweight or obese women - was significantly associated with a lower risk of dementia or MCI. They found similar results in a subsequent study of both men and women (Zeki Al Hazzouri, Stone, Haan, & Yaffe, 2013).

1.5.7 Insulin-Like Growth Factor-1

Insulin-like growth factor (IGF-1) is a hormone involved in the regulation of cell proliferation, cell differentiation, promotion of metabolism (nutrient transport, energy storage, gene transcription and protein synthesis) and programmed cell death in adults (Feldman, Sullivan, Kim, & Russell, 1997; Lauterio, 1992; Pavelic, Matijevic, & Knezevic, 2007). Most circulating IGF-1 is produced by hepatocytes, however many other cell types, including neurons (D’Ercole, Ye, Calikoglu, & Gutierrez-Ospina, 1996) also produce IGF-1, with paracrine or autocrine effects (Croci et al., 2011; Frystyk, 2010; Laron, 2001). Receptors (IGF1R) can be found throughout the body, and have widespread distribution in the brain (D’Ercole et al., 1996). IGF-1 also binds to insulin receptors, though with a lower affinity than to IGF1R. The relationship between IGF-1 bioactivity with insulin levels, insulin resistance and the metabolic syndrome is not straight-forward. There is an inverse U relationship between increasing insulin resistance and IGF-1 activity. Increasing the number of elements of the metabolic syndrome correlates with a peak of IGF-1 activity with three elements but falls thereafter (Brugts et al., 2010).

The function and activity of this hormone can be affected by a number of factors. Activity of IGF-1 is modulated by growth hormone, IGF binding proteins, and IGF receptor resistance (Connor et al, 2008). It is also affected by nutritional factors (Runchey et al., 2012) and physical activity (Bermon, Ferrari, Bernard, Altare, & Dolisi, 1999; Rojas Vega, Knicker,
Hollmann, Bloch, & Struder, 2010). Levels of IGF-1 tend to decrease with age (Laron, 2002; Muller et al., 1993; Sonntag, Ramsey, & Carter, 2005; Toogood, O’Neill, & Shalet, 1996).

Interestingly, some mutations in genes for the insulin/IGF-1 pathway have been linked to increased longevity (Bonafe et al., 2003; Flachsbart et al., 2009; Kojima et al., 2004; Pawlikowska et al., 2009) (Soerensen et al., 2010; Tazearslan, Huang, Barzilai, & Suh, 2011). It is also associated with adiposity. For example, in a cross-sectional study of over 6,000 people Parekh and colleagues (Parekh et al., 2010) found a strong positive correlation of serum IGF-1 levels and adiposity (BMI or waist circumference), and a strong negative correlation with age. Consistent with this, Gapstur and colleagues (Gapstur et al., 2004) showed a positive association between weight and IGF-1 in a 9 year longitudinal study of 1418 adults aged 20 to 34 at enrolment. This is not found in all studies, for Nam and colleagues (Nam et al., 1997) found that obese subjects had similar levels of total IGF-1 compared to the controls, though they did have higher free IGF-1 levels. The association with weight may not be linear, for Gram et al (Gram et al., 2006) showed lower levels of IGF-1 with both low weight and high weight participants compared to mid-weight participants in a study of 2139 women.

Several lines of evidence point to a neuroprotective role for IGF-1, and consequently falling IGF-1 levels with age may reduce some of that protection. Firstly, IGF-1 normally provides neuroprotection by increasing neuronal survival (Carro & Torres-Aleman, 2004). It can also promote β-amyloid clearance from the brain (Carro & Torres-Aleman, 2004; Freude, Schilbach, & Schubert, 2009). There is increasing evidence that cerebral insulin and IGF-1 resistance are major factors in AD (de la Monte, 2012; Talbot et al., 2012).

**Human Studies Relating to IGF-1 and Cognition**

In a cross-sectional study of 22 subjects aged between 65 and 86 years of age by (Rollero et al., 1998) serum IGF-1 levels correlated positively with MMSE scores. Angelini and
colleagues (Angelini et al., 2009) found a similar association in a study of 75 hypertensive patients over 65 years of age. Cognition was measured with MMSE, Cambridge cognitive examination (CAMDEX-R), and the frontal assessment battery (FAB). In a 2 year prospective study by Kalmijn and colleagues (Kalmijn, Janssen, Pols, Lamberts, & Breteler, 2000), a higher IGF-1 level was associated with less cognitive decline among 186 healthy subjects aged 55 to 80 years of age. Dik and colleagues (Dik, Deeg, Visser, & Jonker, 2003) demonstrated that lower IGF-1 levels were associated with poorer information processing speed and a faster decline over three years among 1318 subjects aged 68 – 88 years. In a study of 17 healthy subjects between the age of 66 and 77, Aleman and colleagues (Aleman et al., 2000) found that higher serum IGF-1 levels were associated with better scores in mental processing speed.

Raising IGF-1 levels to treat AD symptoms has shown mixed results. Alvarez et al (Alvarez et al., 2009a) demonstrated that the neurotrophic agent, cerebrolysin, which improves serum IGF-1 levels, also improved global function, disabilities and behavior in 207 late-onset AD patients over a 24 week trial. However Sevigny and colleagues (Sevigny et al., 2008) stimulated production of IGF-1 in a randomized trial of 563 patients with mild to moderate AD over 12 months. No improvement in the treatment group over the controls was observed.

While the research to date suggests that IGF=1 may play a role in AD pathophysiology much more research is needed to determine whether the association is causal, or whether interventions that increase IGF-1 can have neuroprotective effects.

1.5.8 Inflammation

A strong body of evidence shows that systemic low grade inflammation is a common feature of obesity (Bastard et al., 2006; Black, 2002; Das, 2002; Ford, 2003; Wellen & Hotamisligil, 2003), particularly central obesity (Craft, 2007; Fried, Bunkin, & Greenberg, 1998). Epidemiological evidence demonstrates that inflammation is present during cognitive decline
and AD, however it is not clear whether the inflammation is a driving force behind neurological damage, an innocent bystander, or part of a repair process (Bruunsgaard & Pedersen, 2003; Bruunsgaard, Skinhoj, Pedersen, Schroll, & Pedersen, 2000). The relationship between the MetS and risk of cognitive decline may be moderated by inflammatory cytokines such as IL-6, though further research is needed (Yaffe et al., 2004b; Yaffe et al., 2004c). Chronic low-grade inflammation, indicated by biomarkers such as Interleukin (IL)-6 and Tumor Necrosis Factor (TNF)-α becomes increasingly common with age (Bruunsgaard et al., 2000; McGeer, Klegeris, & McGeer, 2005). For example TNF-α increases in the cerebrospinal fluid (CSF) with brain aging, and elevations have been reported in MCI and AD (Carro, Trejo, Gomez-Isla, LeRoith, & Torres-Aleman, 2002; Tarkowski, Andreasen, Tarkowski, & Blennow, 2003). Furthermore TNF-α in the CSF has been shown to antagonize the beneficial increases in β-amyloid clearance that are induced by IGF-1 (Alvarez et al., 2009b; Carro et al., 2002). Free IGF-1 correlates negatively with serum TNF-α (Álvarez, Cacabelos, Sanpedro, García-Fantini, & Aleixandre, 2007; Alvarez et al., 2009b), so elevated TNF-α may contribute to increased β-amyloid load (Craft, 2007). While these findings are suggestive of a link between inflammation and neurocognitive function more research is needed to determine the consistency, magnitude and meaning of the associations.

1.5.9 Cortisol and HPA Axis Dysregulation

Adipose tissue, and particularly central adipose tissue, secretes the glucocorticoid “stress” hormone cortisol (Bjorntorp & Rosmond, 2000; Lottenberg et al., 1998) (Pasquali et al., 1993). However it is now widely believed that in obese individuals cortisol secretion is increased relative to healthy weight controls, but cortisol clearance is also increased, leading to normal or low plasma cortisol concentrations (Morton, Ramage, & Seckl, 2004; Roberge et al., 2007; Salehi, Ferenczi, & Zumoff, 2005). However obesity has been associated with dysregulation of the normal variability of the cortisol diurnal rhythm (Bjorntorp & Rosmond, 2000).
Exposure to glucocorticoids (GCs) such as cortisol can have both direct effects on the brain (McEwen, 2000, 2008; McEwen, Magarinos, & Reagan, 2002). Glucocorticoids readily cross the BBB to act directly on the brain (McEwen, 2000). The effects of these GCs on neurocognitive function depend on the magnitude and duration of exposure (McEwen, 1998, 2004). While mild-moderate exposure can enhance attention and memory, more intense or severe exposure impairs them both (Diamond, Park, & Woodson, 2004; Karlamangla, Singer, Chodosh, McEwen, & Seeman, 2005; McEwen, 1998, 2000; McGaugh & Roozendaal, 2002). Furthermore, elevated GCs are associated with clinical AD symptoms and pathology. For example, patients with early AD may exhibit significantly higher total plasma cortisol than controls (Peskind, Wilkinson, Petrie, Schellenberg, & Raskind, 2001), and higher plasma cortisol predicts more rapid cognitive decline and decreased hippocampal volume (Lupien, Buss, Schramek, Maheu, & Pruessner, 2005a; Lupien et al., 2005b; Peskind et al., 2001; Rasmuson, Nasman, Carlstrom, & Olsson, 2002). Among those without dementia, older adults with significant increases in cortisol over 4 years show deficits in explicit memory, selective attention and an average 14% decrease of hippocampal volume on MRI compared to others with no change or reductions in cortisol (McEwen, 2000). Similarly older women with the highest cortisol levels had the lowest memory scores, and increasing concentrations over a 2.5 year follow-up were associated with cognitive decline (Seeman, McEwen, Singer, Albert, & Rowe, 1997). Building on findings such as these, a glucocorticoid hypothesis of brain aging (Landfield, Blalock, Chen, & Porter, 2007) proposes that repeated stress produces cumulative damage to the brain across the lifespan.

Glucocorticoids can also indirectly affect neurocognitive health via their effects on immune function (McEwen, 1997, 1998; Munck & Naray-Fejes-Toth, 1994), insulin resistance and glucose regulation (Black, 2002; Kyrou & Tsigos, 2007; Wellen & Hotamisligil, 2003, 2005),
Brain-derived neurotrophic factor (BDNF) is a neurotrophin that shows neuroprotective effects in adults. It is involved in learning and memory (Duan, Lee, Guo, & Mattson, 2001b; Lee, Duan, Long, Ingram, & Mattson, 2000; Lu, Christian, & Lu, 2008) in as well as neurogenesis, synaptic plasticity, and neurotransmitter synthesis (Diogenes, Assaife-Lopes, Pinto-Duarte, Ribeiro, & Sebastiao, 2007; Lu, 2003; Mattson, Duan, & Guo, 2003). It is likely that BDNF is involved in the protective cellular repair response after damage (Begliuomini et al., 2008; Mattson, 2005), and it has been found to protect neurons in experimental models of AD and Parkinson's disease (Duan, Guo, & Mattson, 2001a). Increased levels of BDNF are therefore beneficial, but it is difficult to determine whether they reflect good health or the presence of damage that needs repair.

The relationship between obesity and BDNF in humans is not yet clear. In animals, BDNF deficiency leads to hyperphagia, obesity and insulin resistance (Duan, 2003), while central infusion of BDNF in rats induces weight loss due to appetite suppression (Pelleymounter, Cullen, & Wellman, 1995). However the effect of obesity on BDNF is not clear. In humans cross-sectional studies of BDNF and weight give mixed. Some studies find decreased serum BDNF in obese adults relative to controls (Krabbe et al., 2007), yet others have found higher serum BDNF (Suwa et al., 2006). The differences may be due to the populations studied, or to potential confounding factors, as BDNF is affected by gender, age, stress and inflammation among other things (Makar et al., 2008; Makar et al, 2007).

While animal studies show significant effects of central (i.e. brain, CSF) BDNF on brain function, there remains some question as to how well BDNF levels in peripheral circulation...
reflect those in the central nervous system. Few studies have directly addressed this question, but there is some evidence that BDNF does cross the BBB. Poduslo & Curran (Poduslo & Curran, 1996) showed that methionine-BDNF can cross the BBB, though they did not test passage of the natural form of BDNF. In a separate study, Pan and colleagues (Pan, Banks, Fasold, Bluth, & Kastin, 1998) used radiolabelled BDNF in mice and showed that BDNF injected intravenously could be found in the cerebral cortex parenchyma, suggesting passage across the BBB. Conversely, after cerebroventricular injection, radiolabelled BDNF became detectable in blood at a rate similar to that seen for re-absorption of cerebrospinal fluid (CSF). Despite these two studies, the correlations between central and peripheral levels in other studies are mixed. Some researchers have found correlation between serum & cortical BDNF in rats ((Hellweg, Ziegenhorn, Heuser, & Deuschele, 2008; Ziegenhorn et al., 2007). Others have found that serum BDNF correlates positively with cortical BDNF levels in newborn rats, but not in adults (Karege et al., 2002). One study in humans attempted to measure what they hypothesized was BDNF output from the brain using jugular to arterial concentration difference of BDNF in direct, internal jugular vein sampling (Krabbe et al, 2008). However the validity of this methodology is questionable (Lambert, 2008).

Animal studies of BDNF report an important role for BDNF in normal learning and memory (Duan et al., 2001a; Lu et al., 2008; Mattson, 2000; Mu, Li, Yao, & Zhou, 1999). Mice that over-express the BDNF receptor (TrkB) show evidence of enhanced learning and memory (Koponen et al., 2004). Intra-hippocampal administration of BDNF facilitates short-term memory (Alonso et al., 2002), and infusion of anti-BDNF antibodies causes amnesia for spatial learning tasks in rats (Mu et al., 1999). Anti-BDNF antibodies block long-term potentiation (LTP) and impair long-term memory. Transgenic mice deficient in BDNF show deficits in LTP (Croll et al., 1999).
Evidence in humans also indicates an association between BDNF and memory, using measures of BDNF in the peripheral circulation. Interestingly the direction of the association appears to vary with severity of cognitive impairment. Yasutake et al (Yasutake, Kuroda, Yanagawa, Okamura, & Yoneda, 2006a) compared healthy controls to patients with either AD or VaD, matching these patients for age, gender and severity of dementia. Serum BDNF was significantly lower in AD patients than in VaD patients and controls respectively. Despite this, serum BDNF did not correlate with scores on the MMSE or the Functional Assessment Rating Test (FAST) in patients with AD. Similarly Laske et al (Laske et al., 2007; Laske et al., 2006) found that patients with established AD showed the lowest serum BDNF, but BDNF was slightly higher in patients with early stage AD, relative to both normal controls and patients with AD. In this study serum BDNF correlated significantly with MMSE (MCI r=0.855; p=0.001; AD r=0.396; p=0.010). In another study, Zhang and colleagues (2008) found that patients with amnestic MCI had significantly lower circulating BDNF than healthy controls, and that BDNF correlated positively with scores on tests of delayed recall. Genotype for the BDNF gene did not differ between aMCI patients and normal controls, nor did genotype correspond to serum BDNF concentration, indicating that other factors strongly affect BDNF expression. In another study, patients with AD showed lower BDNF than controls in the hippocampus and temporal cortex on autopsy (Yasutake, Kuroda, Yanagawa, Okamura, & Yoneda, 2006b).

In the non-clinical population, BDNF also appears to correlate with cognitive function. For example Komulainen et al (Komulainen et al., 2008), found that decreased BDNF was associated with impaired global cognitive function (CERAD test battery) in women but not men, and with specific impairments in memory but not executive function. In women a one standard deviation decrease in BDNF was associated with 50-60% decreased memory scores, and increased the probability of low MMSE. Effects remained after controlling for age, education,
depression, impaired glucose metabolism, cardiovascular disease, antihypertensive medication, lipid lowering medication, use of sex hormones, smoking, alcohol consumption, storing time of plasma in the freezer and platelet count.

1.6 Summary

Obesity affects a number of factors currently under investigation for their role in dementia pathophysiology, including glucose regulation, inflammation, leptin, IGF-1 and BDNF (Lupien et al., 2005a). Observational studies suggest that midlife obesity can increase risk of cognitive decline or dementia, yet relatively few observational or intervention studies have concurrently investigated the potential mediating role of these mechanistic factors. Most studies have controlled for education, socio-economic status, gender, age and diabetes status, few to date have accounted for the potential role that physical activity, quality of diet or other behaviors linked to obesity could have on the association between obesity and dementia. Hence more research is needed before it can be concluded that obesity plays a causal role in cognitive decline and dementia, and more research is needed to understand the mechanisms that may mediate the effect. Ultimately the best information will be from large, well-controlled randomized controlled trials. However observational studies that account for frequently unmeasured variables such as physical activity or diet can also contribute useful information.

2. Study 2: the NHANES-III Study

2.1 Introduction

Despite a growing body of epidemiological evidence suggesting that midlife obesity increases risk of cognitive decline and dementia later in life (Gustafson, 2008; van den Berg et al., 2008), much remains unknown about the association between obesity and cognitive function in early and mid-adulthood. To better understand the nature of this relationship it will
be important to determine not on the direction of association, but also to investigate whether
duration of obesity affects the association, whether factors such as quality of diet and physical
activity moderate the association, and which physiological mechanisms could mediate the
effect. It is also important to determine whether distribution of body fat plays a role, for the
adipokines secreted by central adipose tissue may confer additional risk of neurocognitive
damage.

The primary aim of this study was to determine whether obesity is associated with
reduced cognitive function in early and mid-adulthood in the general population. Given the
evidence for an association between midlife obesity and cognitive decline ((Gorospe & Dave,
2007; Whitmer et al., 2008), and evidence for prolonged and gradual pre-clinical stages of AD
pathology that predate symptoms by decades (Sperling et al., 2011) it is possible that an
association between obesity and cognitive function is already apparent in midlife. This has been
supported by at least one study (Cournot et al., 2006a), but warrants further investigation.
Assessing dementia risk requires extremely long follow-up times, and it was not be possible to
determine whether such an association reflected an early stage of dementia pathology. Nor was
it possible to determine causal direction. However it is possible to assess whether results are
consistent with what would be expected from a causal association between obesity and later
cognitive decline.

Many studies of the association between obesity and cognitive function have used BMI
as the sole measure of adiposity. Yet at best, BMI is a rough indicator of adiposity, potentially
masking differences in body composition and fat distribution. The mechanisms that may link
obesity to dementia are more closely related to central adiposity than to global obesity, and
studies that differentiated between global and central obesity have tended to show stronger
associations for the latter (Cereda, Sansone, Meola, & Malavazos, 2007; West & Haan, 2009;
Whitmer et al., 2008). The present study therefore investigated the possibility that central obesity, as measured by waist-hip ratio (WHR) is more closely related to cognitive function than global obesity.

Duration of exposure to obesity may be important, since the cumulative effects of small but regular damage could be significant over decades. A cumulative exposure-outcome model of the lifecourse approach to chronic disease etiology (Kuh & Ben-Shlomo, 2004) would predict that prolonged duration of exposure could contribute cumulative effects over time. This study therefore explored whether longer duration of obesity was associated with worse cognitive performance.

If obesity affects cognitive function, then behaviors that affect obesity may affect the association between obesity and cognitive function. Differences in these behaviors could be what really drives the association with obesity, rather than adiposity itself. Alternatively, health-related behaviors may moderate the effects of obesity on neurocognitive health by affecting the physiological mechanisms that increase risk of cognitive decline, such as cardiovascular health, immune function, or levels of neuroprotective factors such as IGF-1 and BDNF. While quality of diet and frequency of PA could affect rates of obesity itself, such that people with good diet and regular PA are less likely to be obese, it is also possible that these factors may have independent effects on cognitive function. Two possibilities present themselves. The association between obesity and cognitive function described elsewhere may simply be an artifact of an effect of poor quality diet and sedentary lifestyle on neurocognitive health. Alternatively, obesity could have an independent effect that can be moderated by good quality diet and regular PA. For example a person who is obese but physically active may have better cognitive function than others who are sedentary. This study therefore investigated whether the association between obesity and cognitive function in midlife was moderated by these health-related behaviors.
Since there is a promising body of evidence supporting a role for physical activity in promoting neurocognitive health (Fratiglioni, Paillard-Borg, & Winblad, 2004; Smith et al., 2010b; Snowden et al., 2011; Stranahan, Zhou, Martin, & Maudsley, 2009b), while the literature on diet is more mixed (Faxén-Irving, Basun, & Cederholm, 2005; Gibson & Green, 2002; Plassman et al., 2010), we hypothesized that PA, but not quality of diet, would moderate the association between obesity and cognitive function in adults.

The present analysis was therefore undertaken to 1) determine whether obesity is associated with cognitive function in the general US population in midlife, and 2) explore factors that may moderate the association, including duration of obesity and health-related behaviors such as diet and PA. The specific aims and hypotheses can be seen in Table 2.1.1.
<table>
<thead>
<tr>
<th>Specific aim</th>
<th>Hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA.1. To determine whether obesity is associated with worse cognitive function in midlife.</td>
<td>H1. Obesity will be associated with worse cognitive function.</td>
</tr>
<tr>
<td>SA.2. To investigate whether central obesity in midlife has a stronger association with cognitive function than global obesity.</td>
<td>H2. The association will be stronger for central obesity (WHR) than for measures of global obesity (BMI, % fat mass).</td>
</tr>
<tr>
<td>SA.3. To investigate whether duration of obesity affects the association with cognitive function.</td>
<td>H3. Obese persons who report they were obese 10 years ago will have worse cognitive function than persons who have been obese less than 10 years.</td>
</tr>
<tr>
<td>SA.4. To determine whether quality of diet and physical activity moderate the association between adiposity and cognitive function.</td>
<td>H4. The association between obesity and cognitive function will remain after adjusting for quality of diet and frequency of physical activity. Physical activity, but not quality of diet, will moderate the association between adiposity and cognitive function.</td>
</tr>
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</table>

Data from the Third National Health and Nutrition Examination Survey (NHANES-III) provides a useful opportunity to investigate whether central obesity or global obesity is associated with minor cognitive deficits in midlife, as well as the potential for health-related behaviors to moderate any such association. Although new NHANES surveys have been conducted since 1994, NHANES-III is the only NHANES study to date to include measures of cognitive function. This secondary data analysis was declared exempt by the Colorado Institutional Review Board. COMIRB Protocol 10-1154
2.2 Methods

2.2.1 Study Design

The Third National Health and Nutrition Examination Survey (NHANES-III) was a cross-sectional epidemiological study of the civilian, non-institutionalized population of the United States. A detailed description of NHANES-III recruitment, sampling and study methods can be found online in the Plan and Operations Manual (NCHS, 1994; U.S. DHHS, 1996). A brief summary of participants, methods and measured variables is provided here.

NHANES-III used a stratified, multi-stage probability sampling design to represent the civilian population in 50 states, based on the 1980 census. Thirteen large counties were chosen and grouped into 34 strata, with 89 sampling locations chosen and further segmented into city and suburban blocks. The detailed approach has been previously described (Miller, 1973; McDowell, 1981). Over the 6 years of the study, 39,695 people were selected for inclusion, 33,994 were interviewed in their homes and were invited to the mobile examination center for medical examinations and follow-up tests. Of these, 78% (30,818) attended the mobile examination centers and 493 others were given examinations in their homes. These home examinations were included in order to gain data from very young children and the very elderly who were unable to visit the mobile examination center. Home examinations included only a subset of the components used at the mobile examination centers.

All participants were interviewed in their homes and given questionnaires to complete. All interviewed participants were invited to attend the mobile examination center for medical exam and further tests. At the mobile examination centers data collection began with a household interview and several questionnaires. These were followed by a medical examination, including the collection of blood and urine specimens. Other tests, such as hearing, vision and the cognitive tests, followed. Staff administering the tests included nurses and clinicians for the
medical and clinical examinations and trained interviewers/research assistants for other tests as appropriate. Standard operating procedures for each test are detailed in the NHANES-III 1988-94 Reference Manuals and Reports (1996).

2.2.2 Participants

Cognitive tests were administered to a sub-sample of adults aged 20-59 years. Assignment to the tests was based on participant number – all participants who had an odd participant number were assigned to the cognitive tests. This produced a sub-sample of 5138 non-institutionalized civilian men and women aged 20-59 years who completed the computerized cognitive test battery. There were no medical or safety exclusions for the cognitive testing component of NHANES-III. However for the purposes of our study, participants were excluded if they did not complete both cognitive tests of interest (SDST and SDLT, described below). Participants were also excluded if they were pregnant, or had evidence of a condition known to affect cognitive function, including vitamin B12 deficiency (<174pg/mL), hypothyroidism (TSH <10 uU/mL), reported a past medical diagnosis of stroke, or reported recent alcohol use (>1 drink in preceding 3hrs). Since physical activity was a key independent variable participants were also excluded if they reported significant difficulty walking ¼ of a mile. The final sample contained 4515 men and women aged 20 – 59 years.

2.2.3 Tests and Materials

Demographics and Medical History

All participants were asked to provide information on their age, gender, education, occupation, income, ethnicity and medical history as part of an in-depth structured interview. Data were recorded at both the NHANES home assessments and at the mobile examination center. The poverty-income ratio (PIR) was computed as a ratio of family income to a composite
variable comprised of poverty threshold, the age of the family reference person, and the calendar year in which the family was interviewed.

**Assessment of Cognitive Function**

Three cognitive tests were administered using the computerized Neurobehavioral Evaluation System (NES). The *Neurobehavioral Testing Manual* details materials and procedures used for tests of cognitive function (DHHS, 1986). However, only two were of interest for the purposes of this study. The simple reaction time test (SRTT) was omitted as speed of tapping was unlikely to be relevant to this study. A summary of the procedures and general results of the cognitive tests have been reported by Krieg et al. (2001). The tests were conducted in a quiet audiometry room of the mobile examination center trailer. Lighting, temperature, environment and test administration were standardized and distractions minimized. Tests were administered on a Compaq 286 Deskpro portable computer with a keyboard overlay to hide unnecessary keys and a joystick. Participants were given the option of taking the tests in English or Spanish. Tests were performed in a fixed order.

The Simple Reaction Time Test (SRTT) is a basic test of motor response speed to a visual stimulus. (Baker, Chrzan, Park, & Saunders, 1985; Krieg et al., 2001; Letz, 1989, 1990).

Respondants rested the index finger of their preferred hand on a push button and were asked to push the button as quickly as possible when they saw a solid square (4 x 4 cm) in the center of the computer screen. When the button was pushed the square disappeared from the screen, and reappeared between 2.5 – 5 seconds later. Each respondent was presented with a total of 50 trials. Responses latency from the time of the square appearing to the time the button was pushed was recorded for each trial and averaged across all trials to produce a summary response (Krieg et al., 2001).
The Symbol Digit Substitution Test (SDST) is a computerized adaptation of the Digit Symbol Substitution Subtest of the WAIS-R (Wechsler, 1981), and is a test of visual motor speed and coding speed (Krieg et al., 2001; Pavlik, Hyman, & Doody, 2004). Nine symbols were presented, paired with 9 digits. Participants were presented with a grid that paired 9 different symbols with the numbers 1 – 9. A similar grid, but with symbols in scrambled order and with the spaces for the digits left blank, was presented at the bottom of the screen (Krieg et al., 2001). Respondents were asked to press a numbered key to match the symbols that were presented in scrambled order lower as quickly as possible. The test contained a practice and 4 trials. The time required to enter each digit and the number of errors were recorded. Responses are in seconds, and higher scores represent worse performance.

Serial Digit Learning Test (SDLT) is reported by the NHANES-III test manual and by Krieg et al. (2001) as a test of learning and memory, but is elsewhere considered a test of attention, concentration or working memory e.g. (Suhr, Stewart, & France, 2004). Participants were asked to learn a series of numbers that were presented slowly (0.6s with 0.6s in-between), one at a time, on the screen. After the numbers were presented, participants used the numbered keys to enter the sequence of numbers they remembered. The practice set involved 4 numbers. Subsequent trials involved a sequence 8 numbers. The test ended when participants recalled two consecutive number sets. Up to 8 trials were presented, each of which repeated the same sequence of numbers. Total score was based on number of incorrect digits in each trial, and the number of trials needed for accurate recall of all 8 numbers. SDLT scores ranged from 0 – 16 and higher scores represent worse SDLT performance.

**Depression**

A sub-sample of participants aged 18 – 39 were given additional questions on history of depression and mania symptoms. After being asked questions about whether they had ever
experienced periods of depressive symptoms they were asked “Are you in one of these spells of feeling low or disinterested and having some of these other problems now?”

**Anthropometric Measures**

Weight, height, waist circumference, and buttock circumference were measured at the NHANES-III mobile examination center (MEC). Waist circumference and buttock circumference were used to calculate the waist-hip ratio (WHR). Bioelectric Impedance Analysis (BIA) was also conducted at the mobile examination center. In BIA, a small and painless electrical current is passed through the body and electrical impedance (ohms) and reactance (ohms) recorded. Body composition was calculated using reactance and impedance ([Lukaski, Johnson, Bolonchuk, & Lykken, 1985]), creating an estimate of percent fat mass (PFM).

In addition to the objective anthropomorphic measures, participants also provided some information on self-reported weight history. For the purpose of this analysis, responses to the question: “How much did you weigh 10 years ago?” were used as an estimate of duration of obesity for participants aged 30-59 years. Responses were given as weight in lbs.

**Laboratory Measures**

Blood was drawn at the NHANES-III mobile examination center for analysis of glucose, insulin, glycosated hemoglobin (HbA1c), triglycerides, cholesterol (HDL, LDL, total), thyroid stimulating hormone (TSH), vitamin B12, C-reactive protein (CRP), and insulin-like growth factor (IGF)-1. A full description of laboratory procedures used for analysis is provided in the Laboratory examination file (U.S. Department of Health and Human Services, 1996). Glycosated hemoglobin measurements for NHANES III were performed by the Diabetes Diagnostic Laboratory at the University of Missouri - Columbia using the Diamat Analyzer System (Bio-Rad Laboratories, Hercules, CA). Insulin-like growth factor 1 was analyzed in 2002 using a sub-set of stored samples (U.S. Department of Health and Human Services, 2003).
Self-Reported Physical Activity

Self-reported physical activity was recorded as part of the adult household questionnaire. Interviewers recorded responses on Likert-type scales to 6 questions on physical activity. These included questions such as “In the past month did you jog or run?” and “In the past month, how often did you jog or run?” This sequence of questions was repeated for a wide variety of different physical activity options, including: ride a bicycle, swim, do aerobics, go dancing, garden or do yard-work, lift weights, or participants could specify other activities. Each activity was assigned an intensity rating (e.g. Jog or run intensity rating [mets]).

Healthy Eating Index

Participants responded to an oral food frequency questionnaire in which they indicated how often they ate various types of food. Researchers at the National Center for Health Statistics compiled dietary responses into a Healthy Eating Index (HEI) for each participant (DHHS, 1996). The HEI is the sum of 10 dietary sub-scales, weighted equally, each of which ranges from 0-10. The HEI is a measure of the quality of dietary composition, rather than caloric intake. High HEI scores indicate dietary intakes close to the recommended ranges or amounts.

Social Support

The Adult Household Questionnaire asked participants about their frequency of social contact with friends, family, neighbors, clubs and organizations or religious organizations.

Smoking Status

Participants were asked a wide range of questions about their use of tobacco products. Based on their responses participants were classified as current smokers if they endorsed questions related to current cigarette, cigar or pipe use, former smokers if they endorsed questions related to former (but not current) cigarette, cigar or pipe use, and never smokers if they indicated they had never made significant use of these tobacco products.
2.2.4 Data Analysis

Due to the complex, multi-stage survey design used in NHANES-III (described above), data were analyzed using SPSS 21 Complex Samples (IBM). The standardized weighting and estimation methodology for NHANES-III are available for download on the NCSH website. Strata (SDPSTRA6), cluster (SDPPSU6), and sample weights (WTPFCNS6) specific to the cognitive subsample were applied.

Table 2.2.1. Pre-existing categorical variables already created in NHANES dataset.

<table>
<thead>
<tr>
<th>Variable</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Male~</td>
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<td></td>
<td>Female</td>
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<tr>
<td>Ethnicity</td>
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<td></td>
<td>Non-Hispanic Black</td>
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<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Depression now</td>
<td>Yes</td>
</tr>
</tbody>
</table>
|                         | Currently
experiencing
depressed symptoms |
|                         | No~             |
|                         | Not currently
experiencing. |

Note. ~ Reference group in regression analyses.

Calculation of New Variables

To facilitate analysis, calculation of new categorical variables was performed where necessary. Categories of BMI were created according to the World Health Organization criteria (WHO, 2006), as can be seen in Table 2.2.2. Participants were considered obese if BMI was ≥30, overweight if BMI was 25-29.9, and a healthy weight if BMI was between 18.5 and 24.9. A dichotomous variable for central obesity (yes/no) was also created using criteria used by the World Health Organization in their definition of the metabolic syndrome (WHO, 1998). Central
obesity was defined as a WHR ≥0.90 for men, or ≥0.85 for women. Duration of obesity was estimated using participants’ responses to the question “How much did you weigh 10 years ago?” Responses, given as weight in lbs, were used by the author to calculate the respondent’s estimated BMI 10 years ago. This was done with the assumption that for most persons aged 30-59 years height would not have changed much over the course of 10 years. Participants younger than 30 at the time of the NHANES study were excluded from this sub-analysis since they may not have reached their adult height 10 years prior. The author then created a categorical variable to classify participants into 3 groups: 1) persons who were obese at both time points, 2) participants who were not obese at time 1, but were obese at time 2, and 3) participants who were not obese at either time point. Obesity was assessed using BMI alone, as it was not possible to estimate WHR 10 years ago from the data available.

Categorical variables for physical activity, social support and smoking status were also created. The estimate of self-reported frequency of physical activity was recorded as follows. Based on participants’ self-reported frequency of leisure time physical activity and the activity intensity rating encoded in the NHANES dataset (mets), we categorized participants as either sedentary (engaging in activity of at least 3 mets <4 times per month), moderately active (activity of at least 3 mets 5-19 times per month) or active (activity of at least 3 mets >20 times per month). The dichotomous variable for social support was categorized on the basis of responses to two questions on frequency of contact with family or friends. Persons who reported they were not married and had <1x per week on the phone with family or friends were classified as having “little” social support, while all other participants were classified as “some”. Smoking status was calculated based on responses to multiple questions on tobacco use. Participants who reported that they smoke cigarettes, pipe, cigars or use chewing tobacco or snuff now were classified as current smokers.
Dummy variables were created for all categorical variables. Reference groups are indicated in results tables below. Cognitive measures, age, education and all biomarkers (HbA1c, CRP, IGF-1, BP, HDL) were entered as continuous variables, consistent with other analyses of similar data.
Table 2.2.2. New categorical variables created for this analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity</td>
<td>Yes  Men WHR ≥ 0.9, Women WHR ≥ 0.85</td>
</tr>
<tr>
<td></td>
<td>No~ Men WHR &lt; 0.9, Women WHR &lt; 0.85</td>
</tr>
<tr>
<td>BMI categories</td>
<td>Healthy weight~ BMI 18.5 - 24.9</td>
</tr>
<tr>
<td></td>
<td>Overweight BMI 25 – 29.9</td>
</tr>
<tr>
<td></td>
<td>Obese BMI ≥30</td>
</tr>
<tr>
<td>Obesity duration</td>
<td>10+ years Obese at interview and 10 years before</td>
</tr>
<tr>
<td></td>
<td>&lt;10 years Obese at time interview only</td>
</tr>
<tr>
<td></td>
<td>Not obese~ Not obese at 1 or 2</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Sedentary~ ≤ 4 times per month</td>
</tr>
<tr>
<td></td>
<td>Moderately active 4 – 19 times per month</td>
</tr>
<tr>
<td></td>
<td>Active ≥ 20 times per month</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Current smoker Use cigarettes, pipe, cigars, chewing tobacco or snuff now</td>
</tr>
<tr>
<td></td>
<td>Former smoker Not current, but have ever smoked 100+ cigarettes, 20+ pipes</td>
</tr>
<tr>
<td></td>
<td>etc.</td>
</tr>
<tr>
<td></td>
<td>Never smoked~ Not current or former.</td>
</tr>
<tr>
<td>Social support</td>
<td>Little Not married, &lt; 1 phone contact with family or friends per week.</td>
</tr>
<tr>
<td></td>
<td>Some~ Married or greater than 1 contact with family or friends per week.</td>
</tr>
</tbody>
</table>

Note. ~ Reference group in regression analyses.

Approximately 75% of participants meeting inclusion criteria for this study did not report their income, preventing the calculation of the poverty-income ratio. This variable was
therefore excluded from analysis. Only 476 of participants with responses to depression questions (depressed or not) met our inclusion criteria. To avoid loss of statistical power, a separate sub-sample analysis was run for persons with depression data.

Regression Diagnostics

Before conducting regression modeling, the distribution of each variable was examined visually using frequency histograms and scatter plots, and Cook’s distance and leverage values were used in the assessment of outliers. Seven participants with extreme WHR (e.g. 2.0) greater than 3 standard deviations (sd) from the mean were excluded from analyses due to their potential to unduly affect regression results. Regression diagnostics were conducted to check for linearity, normality and multicollinearity. To check that the distribution of the dependent variables was normal, with a constant variance, for each combination of values of the independent variables and covariates, scatter plots of predicted versus observed values and residuals plots (studentized, studentized deleted) were assessed. Results of the symbol digit substitution test (SDST) were positively skewed and scores required a natural log transformation to achieve better approximation of a normal distribution. Pre-model screening of scatter plots was conducted to determine the linear association between each covariate or independent variable and cognitive outcome measure. Checks for multicollinearity were made using tolerance scores, and correlation coefficients used to check bivariate correlations between key variables.

Regression Model-Building

Separate multiple regression analyses were used to test the associations between each of the 2 cognitive variables of interest (SDST or SDLT) and the 3 different measures of adiposity (BMI, WHR or % fat mass) to determine if central obesity or global obesity differed in their association with cognitive function. Regression model building followed the purposeful
hierarchical model-building approach described by Kleinbaum et al (2008). First, sociodemographic variables (age, gender, ethnicity, education) were entered as a set. Second, measures of adiposity were entered separately to allow for comparison of models: BMI alone, WHR alone or percent fat mass alone. Significance of the parameter estimate, and the contribution to proportion of variance explained, were evaluated. Keeping these variables in the model, the health-related behavior (PA, diet, smoking, social support) variables were each added to the model, to determine main effect. Next, interaction terms between behavioral variables and the relevant adiposity variable for that model (e.g. PA x WHR) were entered to assess potential moderation of the association between adiposity and cognitive score. Finally, the model was adjusted for biomarkers that are potential mediators of an association between obesity and cognitive function, including CRP, HbA1c, blood pressure, and cholesterol.

2.3 Results

2.3.1 Sample Characteristics

The final sample included 4515 adults aged 20 – 59 years (mean=36.95 years). As seen in Table 2.3.1, 50.5% were women, and the sample included 77.2% non-Hispanic whites, 11% African Americans, 5.2% Mexican Americans and 6.5% other ethnicities. The average level of education in the sample was 12.86 years (sd = 0.08). Obese participants (BMI>30) represented 22.5% of the sample, while 31.7% were overweight (BMI 25 - 29.9) and 45.9% were in the healthy weight range (BMI 18.5 - 24.9) (WHO, 2006). Consistent with the hypothesis that central obesity is distinct from overall obesity, more than half of the sample (53.8%) met criteria for central obesity (WHO, 1998) based on waist-hip ratio (WHR), including 14.9% in the healthy BMI range, and 22.2% who were overweight according to the BMI. Mean percent fat mass and WHR for each BMI category can be seen in Table 2.3.1. Correlations between BMI, percent fat mass and waist-hip ratio are displayed in Table 2.3.2. Increasing age was associated with higher waist-
hip ratio \((p<0.000)\), higher BMI \((p<0.000)\) and higher proportion of fat mass \((p<0.000)\). Being female was associated with greater adiposity \((p<0.000)\). Higher education was associated with less adiposity in each of these measures \((p<0.000)\). As previously described, participant SES (poverty-income ratio) was not assessed due to high non-response rates for the income variable and the potential for non-response bias.

Quality of diet, as estimated by the Healthy Eating Index (HEI) score was 62.39 across all participants. Higher scores indicate better quality diet. As shown in Figure 2.3.1, mean HEI scores were similar for the healthy weight, overweight and obese groups. The correlation between quality of diet and frequency physical activity was low \((R^2=-0.049)\). Current smokers composed 35.5% of the sample, former smokers 20.9% and never smokers made up 43.6% of the sample. Among the sample of participants who completed the cognitive tests, 476 participants aged 20 – 39 completed the Diagnostic Interview Schedule that assessed depression. Of these 129 persons reported that they were experiencing a spell of feeling low now.
Table 2.3.1. NHANES-III sample characteristics by BMI category.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Healthy Weight</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (n)</td>
<td>4515</td>
<td>1842</td>
<td>1463</td>
<td>1210</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.05</td>
<td>34.63</td>
<td>38.74</td>
<td>39.59</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.85</td>
<td>13.13</td>
<td>12.79</td>
<td>12.35</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>50.2</td>
<td>20.9</td>
<td>19.5</td>
<td>9.8</td>
</tr>
<tr>
<td>Female (%)</td>
<td>49.8</td>
<td>24.9</td>
<td>12.2</td>
<td>12.8</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White (%)</td>
<td>76.9</td>
<td>36.5</td>
<td>24.3</td>
<td>16.1</td>
</tr>
<tr>
<td>Non-Hispanic Black (%)</td>
<td>11.1</td>
<td>4.3</td>
<td>3.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Mexican American (%)</td>
<td>5.3</td>
<td>1.8</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Other (%)</td>
<td>6.7</td>
<td>3.0</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Adiposity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (continuous)</td>
<td>26.67</td>
<td>22.21</td>
<td>27.11</td>
<td>35.12</td>
</tr>
<tr>
<td>% Fat mass</td>
<td>30.14</td>
<td>25.90</td>
<td>30.44</td>
<td>38.45</td>
</tr>
<tr>
<td>WHR (continuous)</td>
<td>0.89</td>
<td>0.85</td>
<td>0.92</td>
<td>0.94</td>
</tr>
<tr>
<td>Centrally obese (%)</td>
<td>54.8%</td>
<td>14.9%</td>
<td>22.2%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Cognitive function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln (SRTT)^</td>
<td>3.08</td>
<td>3.04</td>
<td>3.11</td>
<td>3.14</td>
</tr>
<tr>
<td>SDLT^</td>
<td>4.36</td>
<td>3.77</td>
<td>4.68</td>
<td>5.11</td>
</tr>
<tr>
<td>Ln(SDST) (s) ^</td>
<td>3.08</td>
<td>3.04</td>
<td>3.11</td>
<td>3.12</td>
</tr>
<tr>
<td>Health-related behaviors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active (%)</td>
<td>56.6</td>
<td>29.0</td>
<td>17.9</td>
<td>9.7</td>
</tr>
<tr>
<td>Some activity (%)</td>
<td>22.9</td>
<td>9.1</td>
<td>6.7</td>
<td>7.1</td>
</tr>
<tr>
<td>Sedentary (%)</td>
<td>20.5</td>
<td>7.7</td>
<td>7.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Healthy Eating Index</td>
<td>62.39</td>
<td>62.83</td>
<td>62.86</td>
<td>61.12</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked (%)</td>
<td>43.4</td>
<td>19.6</td>
<td>13.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Former smoker (%)</td>
<td>21.3</td>
<td>8.9</td>
<td>6.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>35.3</td>
<td>17.2</td>
<td>11.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Biomarkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.23</td>
<td>5.07</td>
<td>5.26</td>
<td>5.54</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.37</td>
<td>0.31</td>
<td>0.34</td>
<td>0.54</td>
</tr>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>286.84</td>
<td>300.72</td>
<td>285.11</td>
<td>260.04</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>117.87</td>
<td>113.70</td>
<td>119.33</td>
<td>124.29</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.30</td>
<td>1.42</td>
<td>1.23</td>
<td>1.14</td>
</tr>
<tr>
<td>Depressive symptoms now (n)</td>
<td>24.2</td>
<td>14.1</td>
<td>3.3</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Notes: ^ Higher scores indicate worse performance.
Based on self-reported frequency and intensity of leisure time physical activity 56.4% of the sample were active (20 or more times a month), 22.9% were moderately active (4 – 19 times a month), and 20.7% met study criteria for being sedentary (<4 times per month). Correlations between self-reported physical activity and measures of adiposity were low, as shown in Table 2.3.2.

<table>
<thead>
<tr>
<th></th>
<th>Body Mass Index</th>
<th>Waist-Hip Ratio</th>
<th>Percent fat mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass Index</td>
<td>1</td>
<td>0.412</td>
<td>0.645</td>
</tr>
<tr>
<td>Waist-Hip Ratio</td>
<td>0.412</td>
<td>1</td>
<td>0.019</td>
</tr>
<tr>
<td>Percent fat mass</td>
<td>0.645</td>
<td>0.019</td>
<td>1</td>
</tr>
<tr>
<td>Physical activity</td>
<td>0.119</td>
<td>0.084</td>
<td>0.183</td>
</tr>
<tr>
<td>Healthy Eating Index</td>
<td>-0.013</td>
<td>-0.057</td>
<td>0.025</td>
</tr>
<tr>
<td>Smoking status</td>
<td>-0.071</td>
<td>0.159</td>
<td>-0.173</td>
</tr>
</tbody>
</table>

2.3.2 Regression Model-building process

Regression analyses were run separately for the SRTT, SDLT and SDST. The regression model-building process involved the following 5 steps for each of these models.

**Model 1.** In the first step all the demographic variables were entered together. These variables were retained in the model irrespective of whether they were significant predictors of cognitive function.

**Model 2.** Next, a measure of adiposity was added to the model, and its association with the outcome variable assessed. If there was no association the model-building process ended at this step for that particular measure of adiposity. If it was significant the model-building process continued on to model 3.

**Model 3.** Next, the behavioral variables were added to the model to create a main effects model.

**Model 4.** Whether or not any of the main effects of those behavioral variables were significant predictors of cognitive function, the interaction terms were also added to the model.
Model 5. Finally, the potential mediating biomarkers were added to the model.

2.3.3 Regression Models of the Simple Reaction Time Test

The SRTT is a test of simple motor response speed. Higher scores on the SRTT test represent longer time (seconds) to task completion, and hence worse performance. The distribution of the variable was skewed, so was adjusted using a natural log transformation. All results below refer to the log transformed values.

SRTT Model 1: Demographic Variables

As has been reported elsewhere with this dataset (Krigg et al, 2001), after log transformation to increase approximation towards normality, the SRTT (ln(SRTT)) scores were significantly associated with demographic factors. Increasing age was associated with worse SRTT performance, \( p<0.001 \). Lower education was related to worse performance on the SRTT \( p<0.000 \). Gender was also a significant predictor of SRTT score, with women performing the test approximately 0.05 ms faster than men. African Americans and Mexican Americans performed slightly slower on the SRTT than non-Hispanic whites. However it was not possible to conduct planned adjustments for socio-economic status using the poverty-income ratio due to large amounts of missing data. It is likely that this is an artifact attributable to other unmeasured variables such as socio-economic status.

All subsequent regression analyses were adjusted for age, sex, education and ethnicity, which were entered in the first step of the regression model building process. The model with all four of these demographic variables entered simultaneously accounted for 9.1% of the variance in SRTT score. Women had faster reaction times than men.
SRTT Model 2: Adiposity Measures

To determine whether increased adiposity was associated with increased reaction time, regression analyses were performed for 3 separate models with different measures of adiposity. Model 2a assessed the association between BMI and SRTT. Model 2b assessed the association between percent body fat and SRTT. Model 2c assessed the association between WHR and SRTT. The results of the three models are presented in Table 3.3.3. All models are adjusted for age, education, gender and ethnicity.

Model 2a (BMI): As can be seen in Table 3.3.3., higher BMI was associated with higher SRTT scores, indicating poorer performance. Controlling for demographic variables, a 1 point increase in BMI increased SRTT score by 0.001 (SE=0.001, p=0.040). The model including BMI accounted for only 9.3% of the variance in SRTT, adding only 0.2% to the demographics only model.

Model 2b (%fat): In contrast to BMI, higher proportion of body fat was not associated with increased SRTT scores (β=0.001, SE=0.001, p=0.173).

Model 2c (Central obesity): Increasing WHR was associated with higher SRTT scores, indicating worse performance (β =0.110, SE=0.050, p=0.034). The range for WHR is between 0.7 – 1.5, therefore for every 0.1 point increase in WHR, the SRTT score increased by 0.011 points. The regression model with WHR accounted for 9.2% of the variance in SRTT score, adding only 0.1% to the demographics only model.
Table 2.3.3. Multiple Linear Regression models of the association between measures of adiposity and SRTT. 

<table>
<thead>
<tr>
<th>Variable</th>
<th>BMI</th>
<th></th>
<th></th>
<th>% Fat Mass</th>
<th></th>
<th>WHR</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>P</td>
<td>β</td>
<td>SE</td>
<td>P</td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>Education</td>
<td>-.010</td>
<td>.001</td>
<td>.000</td>
<td>-.009</td>
<td>.002</td>
<td>.000</td>
<td>-.009</td>
<td>.001</td>
</tr>
<tr>
<td>Age</td>
<td>.001</td>
<td>.000</td>
<td>.006</td>
<td>.001</td>
<td>.000</td>
<td>.005</td>
<td>.001</td>
<td>.000</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male~</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>.062</td>
<td>.008</td>
<td>.000</td>
<td>.056</td>
<td>.008</td>
<td>.000</td>
<td>.073</td>
<td>.010</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White~</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>.045</td>
<td>.008</td>
<td>.000</td>
<td>.045</td>
<td>.008</td>
<td>.000</td>
<td>.050</td>
<td>.007</td>
</tr>
<tr>
<td>Hispanic</td>
<td>.036</td>
<td>.009</td>
<td>.000</td>
<td>.036</td>
<td>.009</td>
<td>.000</td>
<td>.036</td>
<td>.009</td>
</tr>
<tr>
<td>Other</td>
<td>.022</td>
<td>.017</td>
<td>.188</td>
<td>.020</td>
<td>.017</td>
<td>.232</td>
<td>.027</td>
<td>.018</td>
</tr>
<tr>
<td>Adiposity measure</td>
<td>.001</td>
<td>.001</td>
<td>.040</td>
<td>.001</td>
<td>.001</td>
<td>.173</td>
<td>.110</td>
<td>.050</td>
</tr>
<tr>
<td>Model R²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.093</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.092</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model R²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: ^ Natural log of milliseconds. Higher scores indicate worse performance. Each model was run separately. ~ Coded as the reference group for the dummy variable. Other scores within this variable are relative to this group.

SRTT Model 3: Is the association Between Obesity and SRTT Moderated by Health Behaviors?

Health related behaviors were added as a block to determine whether they moderated the association between adiposity and SRTT performance. This was conducted for the BMI and WHR models only, since % fat mass was not associated with SRTT performance.

SRTT Model 3a (BMI): After adjusting for quality of diet, smoking status, social support and physical activity BMI was no longer significantly associated with SRTT score (p=0.075). Neither quality of diet nor smoking status was associated with SRTT scores. Being sedentary was associated with HEI score β=-0.022, SE=0.007, p=0.005). Having little social support was also associated with worse SRTT performance. The health behavior model accounted for only 9.9% of the variance in SRTT.

SRTT Model 3c (central obesity): After adjusting for health-related behaviors, WHR remained a significant predictor of SRTT score (β=0.102, SE=0.05, p=0.047), though the model accounted for only 10.2% of the variance in SRTT. As with BMI, quality of diet (HEI) was not
associated with SRTT scores (β=-0.000, SE=0.00, p=0.212). Nor was smoking status associated with SRTT performance. However being sedentary (β=-0.0.025, SE=0.0.008, p=0.002) or doing some activity (β=-0.0.012, SE=0.0.008, p=0.032) was associated with worse performance relative to active participants. Having little social support was not associated with SRTT performance.

**SRTT Model 4: Interaction Models of Health Behaviors:** To assess the potential for moderating effects of health-related behaviors on the association between adiposity and SRTT performance, interaction terms between each of the behaviors and measures of adiposity were entered into the respective models. Each interaction term was entered separately and together with the other terms. To facilitate interpretation of interaction terms, interaction models were run using categorical variables for the measures of adiposity – that is interaction models were run for categorical measures of BMI and central obesity.

*SRTT Model 4a (BMI):* No interactions between BMI categories (healthy, overweight, and obese) were significant predictors in the model. Similarly, no interaction terms were statistically significant for *Model 3 (Central obesity).* Interaction terms for health behavior were therefore excluded from the ongoing model-building process.
**SRTT Model 5: Potential Factors Mediating the Association Between Adiposity and SRTT**

To test the hypothesis that the association between adiposity and cognitive function is mediated by physiological mechanisms potentially linked to cognitive function and adiposity, biomarkers were next added to the model. Building on the behavioral model (containing no interaction terms), biomarkers were added to the model to determine whether the associations between adiposity and SRTT was mediated by physiological factors. Biomarkers added included HbA1c, CRP, IGF-1, systolic blood pressure, and HDL cholesterol. None of the variables were associated with change in SRTT score, for either adiposity model (BMI or WHR), nor did their inclusion, or removal, appreciably alter the direction or magnitude of the associations already found between SRTT and other variables.

---

| **Table 2.3.4. Multiple linear regression model of the association between central obesity (WHR) and reaction time (SRTT).**^ |  |
|---|---|---|
| **Central obesity** | **β** | **SE β** | **P** |
| Age | .001 | .000 | .053 |
| Education | -.009 | .002 | .000 |
| Gender | - | - | - |
| Male~ Female | .067 | .009 | .000 |
| Ethnicity | - | - | - |
| Non-Hispanic White~ Non-Hispanic Black | .048 | .008 | .000 |
| Hispanic Other | .029 | .010 | .005 |
| .024 | .019 | .208 |
| WHR | .102 | .050 | .047 |
| Healthy Eating Index | - | - | - |
| Sedentary | .022 | .007 | .005 |
| Moderately active | .018 | .008 | .028 |
| Active~ | - | - | - |
| Social support | - | - | - |
| Little | .031 | .014 | .036 |
| Some | - | - | - |
| Model R2 = 9.6 |

**Notes:** ^Natural log transformed. ~ Reference group.
2.3.4 Regression Models of the Symbol Digit Substitution Test

The SDS is a test of visuomotor speed and coding speed (Krigg et al, 2001; Wechsler, 1981). Higher scores on the SDST test represent longer time (seconds) to task completion, and hence worse performance.

SDST Model 1: Demographic Variables

As has been reported elsewhere with this dataset (Krigg et al, 2001), after log transformation to increase approximation towards normality, the SDST (ln(SDST)) scores were significantly associated with demographic factors. Increasing age was associated with worse cognitive test performance, with age independently accounting for 19% of the variance in SDST (p<0.000). Lower education was related to worse performance on the SDST, accounting for 23% of the variance in SDST (p<0.000). Gender was also a significant predictor of SDST score. As can be seen in Table 2.3.5, SDST test scores differed by ethnicity, but since it was not possible to conduct planned adjustments for socio-economic status using the poverty-income ratio due to large amounts of missing data it remains likely that this is an artifact attributable to other unmeasured variables such as socio-economic status. All subsequent regression analyses were adjusted for age, sex, education and ethnicity, which were entered in the first step of the regression modeling. The model with all four of these demographic variables entered simultaneously accounted for 46.6% of the variance in SDST score.

SDST Model 2: Is Adiposity Related to SDST Performance?

To test the hypothesis that higher adiposity, particularly central adiposity, is related to cognitive function in midlife measures of adiposity were added to the demographic factor model described above. Three separate models with different measures of adiposity were run to determine whether central obesity (WHR) showed a different association with cognitive function than global obesity.
**SDST Model 2a (BMI):** The inclusion of BMI in the model had no significant effect on variance explained, nor was the coefficient significantly associated with SDST test performance.

**SDST Model 2b (%fat):** The inclusion of percent fat mass had no significant effect on variance in SDST explained, nor was the coefficient significantly associated with SDST test performance.

**SDST Model 2c (Central obesity):** As with other measures of adiposity, WHR was not significantly associated with SDST test performance, and its inclusion in the model did not alter variance explained.

**SDST Model 3. Do Behavioral Factors Moderate the Association with Obesity?**

Regression analyses were planned to investigate the potential moderating effect of health-related behaviors on the association between obesity and cognitive function in midlife. However since performance on the SDST was not associated with any measure of adiposity potential moderators of the effect are not reported.
Table 2.3.5.  Multiple linear regression models of the association between measures of adiposity and measures of cognitive function. SDLT (total score) or SDST (natural log of seconds). Each model was run separately.

<table>
<thead>
<tr>
<th>SDST^a</th>
<th>BMI</th>
<th>% Fat Mass</th>
<th>WHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.010</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male^†</td>
<td>.065</td>
<td>.008</td>
<td>.000</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White^†</td>
<td>.014</td>
<td>.007</td>
<td>.000</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td></td>
<td></td>
<td>.105</td>
</tr>
<tr>
<td>Hispanic</td>
<td>.085</td>
<td>.014</td>
<td>.079</td>
</tr>
<tr>
<td>Other</td>
<td>.087</td>
<td>.020</td>
<td>.083</td>
</tr>
<tr>
<td>Education</td>
<td>-.037</td>
<td>.002</td>
<td>-.037</td>
</tr>
<tr>
<td>Adiposity measure</td>
<td>.000</td>
<td>.001</td>
<td>.557</td>
</tr>
</tbody>
</table>

Model R² = .466  
Model R² = .463  
Model R² = .469

<table>
<thead>
<tr>
<th>SDLT^a</th>
<th>BMI</th>
<th>% Fat Mass</th>
<th>WHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.081</td>
<td>.007</td>
<td>.000</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male^†</td>
<td>.094</td>
<td>.163</td>
<td>.565</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White^†</td>
<td>1.813</td>
<td>.176</td>
<td>.000</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td></td>
<td></td>
<td>.175</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.475</td>
<td>.308</td>
<td>.000</td>
</tr>
<tr>
<td>Other</td>
<td>2.594</td>
<td>.476</td>
<td>.000</td>
</tr>
<tr>
<td>Education</td>
<td>-.580</td>
<td>.031</td>
<td>-.578</td>
</tr>
<tr>
<td>Adiposity measure</td>
<td>.029</td>
<td>.013</td>
<td>.035</td>
</tr>
</tbody>
</table>

Model R² = .249  
Model R² = .248  
Model R² = .251

Notes: ^Higher scores indicate worse performance. †Coded as the reference group for the dummy variable. Other scores within this variable are relative to this group.

2.3.5 Regression Models of the Serial Digit Learning Task

The SDLT requires participants to learn and recall a sequence of 8 numbers. Total score was based on number of incorrect digits in each trial, and the number of trials needed for accurate recall of all 8 numbers. SDLT scores ranged from 0 – 16 and higher scores represent worse SDLT performance.

SDLT Model 1: Demographic Variables

As has been reported elsewhere with this sample (Krigg et al, 2001), performance on the SDLT was significantly associated with demographic factors. Lower education was related to
poorer performance, accounting for 16.8% of the variance in SDLT (p<0.000). While age accounted for only 3.2% of the variance in SDLT with the sample size this was statistically significant (p<0.000). Gender was not a significant predictor of SDLT, but was retained in the model due to its potential for association with independent variables to be added in subsequent steps. As can be seen in Table 2.3.5, SDLT scores were related to ethnicity, but due to missing data in variables such as the poverty-income ratio it was not possible to adjust for socio-economic status. All subsequent regression analyses were adjusted for age, sex, education and ethnicity. Together the demographic variables accounted for 24.4% of the variance in SDLT.

**SDLT Model 2: Is There an Association Between Adiposity and SDLT Performance?**

To determine whether central obesity or global obesity have different associations with cognitive function, three separate models were run, each with a different measure of adiposity. Model 1 assessed the association between BMI and SDLT. Model 2 assessed the association between percent body fat and SDLT. Model 3 assessed the association between WHR and SDLT. The results of the three models are presented in Figure C.3.3. All models are adjusted for age, education, gender and ethnicity.

**SDLT Model 2a (BMI):** As can be seen in Figure C.3.3., higher BMI was associated with higher SDLT scores, indicating poorer performance. Controlling for demographic variables, a 1 point increase in BMI increased SDLT score by 0.029 (SE=0.013, p=0.035). The model including BMI accounted for 24.9% of the variance in SDLT.

**SDLT Model 2b (%fat):** Higher proportion of body fat was associated with increased SDLT scores, such that each 1% increase in fat mass was associated with a 0.035 point increase in SDLT score (SE=0.013, p=0.013). The total model accounted for 24.8% of the variance in SDLT.

**SDLT Model 2c (Central obesity):** Increasing WHR was associated with higher SDLT scores, indicating worse performance (β =5.56, SE=1.89, p=0.005). The range for WHR is
between 0.7 – 1.5, therefore for every 0.1 point increase in WHR, the SDLT score increased by 0.556 points (SE=0.19, p=0.005). The regression model with WHR accounted for 25.1% of the variance in SDLT score.

**Do Health Behaviors Moderate the Association Between Adiposity and SDLT?**

To test the hypothesis that health-related behaviors moderate the association between adiposity and cognitive function, hierarchical regression model-building was conducted to determine whether the association between SDLT performance and adiposity was moderated by interactions with modifiable health-related behaviors.

**SDLT Model 3. Main Effects Models of Health-Related Behaviors and SDLT**

*SDLT Model 3a (BMI):* After adjusting for quality of diet, smoking status, social support and physical activity BMI was no longer associated with SDLT score (p=0.081). By contrast, better quality diet (higher HEI) was associated with lower (better) SDLT scores (β=−0.017, SE=0.006, p=0.008). Former smokers showed better SDLT performance than persons who had never smoked (β=−0.888, SE=0.231, p=0.000). No significant association was found for current smokers. Having little social support was not associated with SDLT performance. Physical activity was not associated with SDLT performance. The health behavior model accounted for 25.8% of the variance in SDLT.

*SDLT Model 3b (%fat):* In contrast to BMI, percent fat remained a significant predictor of SDLT performance after adjusting for health-related behaviors. (β=0.034, SE=0.014, p=0.015). The model accounted for 26.0% of the variance in SDLT score.

*SDLT Model 3c (central obesity):* After adjusting for health-related behaviors, WHR remained a significant predictor of SDLT score (β=5.456, SE=1.913, p=0.006). The model accounted for 26.5% of the variance in SDLT. As with BMI, better quality of diet (higher HEI) was associated with better (lower) SDLT scores (β=−0.016, SE=0.006, p=0.005). Former smokers...
showed better SDLT performance than persons who had never smoked ($\beta=-0.858$, SE=0.237, $p=0.001$). No significant association was found for current smokers. Having little social support was not associated with SDLT performance. Physical activity was not associated with SDLT performance.

**SDLT Model 4: Interactions Between Health-Related Behaviors and SDLT**

To assess the potential for moderating effects of health-related behaviors on the association between adiposity and SDLT performance, interaction terms between each of the behaviors and measures of adiposity were entered into the respective models. Each interaction term was entered separately and together with the other terms. To facilitate interpretation of interaction terms, interaction models were run using categorical variables for the measures of adiposity. Interaction models were therefore run only for categorical measures of BMI and central obesity.

**SDLT Model 4a (BMI):** No interactions between BMI categories (healthy, overweight, and obese) were significant predictors in the model.

**SDLT Model 4c (Central obesity):** Interactions between quality of diet, smoking status or social support did not contribute significantly to the model, nor did they significantly change the significance of other variables when removed. By contrast, the interaction between central obesity and physical activity was significant ($p=0.05$). The interaction terms that were not statistically significant were removed from the model, as was the main effect of social support, which remained non-significant. The physical activity interaction model accounted for 25.8% of the variance in SDLT, and is presented in Table 2.3.6. As in the main effects model, better quality of diet remained associated with better (lower) SDLT scores ($\beta=-0.017$, SE=0.006, $p=0.009$). Similarly, former smokers continued to show better SDLT performance than persons who had never smoked ($\beta=-0.859$, SE=0.226, $p=0.000$).
Figure 2.3.1. Interaction between central obesity and physical activity for SDLT performance.
Table 2.3.6. Multiple linear regression model of the association between central obesity and SDLT (total score).

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>SE β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.086</td>
<td>0.847</td>
<td>0.000**</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>0.054</td>
<td>0.176</td>
<td>0.759</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>1.78</td>
<td>0.195</td>
<td>0.000**</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.369</td>
<td>0.328</td>
<td>0.000**</td>
</tr>
<tr>
<td>Other</td>
<td>2.412</td>
<td>0.454</td>
<td>0.000**</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central obesity</td>
<td>-0.544</td>
<td>0.037</td>
<td>0.000**</td>
</tr>
<tr>
<td>Healthy Eating Index</td>
<td>-0.017</td>
<td>0.006</td>
<td>0.000**</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Former smoker</td>
<td>-0.859</td>
<td>0.226</td>
<td>0.000**</td>
</tr>
<tr>
<td>Current smoker</td>
<td>-0.341</td>
<td>0.211</td>
<td>0.112</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Moderately active</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Active</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Interaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA x central obesity</td>
<td>-0.714</td>
<td>-2.063</td>
<td>0.044</td>
</tr>
<tr>
<td>Centrally obese &amp; sedentary</td>
<td>-0.971</td>
<td>-3.331</td>
<td>0.002</td>
</tr>
<tr>
<td>Centrally obese &amp; moderate</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Centrally obese &amp; active</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\[Model \, R^2 = 0.258\]

Note: ^ Higher scores indicate worse performance. * Statistically significant at p<0.05. ** Statistically significant at p<0.001.

Closer investigation of the interaction between central obesity and physical activity, shown in Figure D.3.1, indicated that among participants who were not centrally obese, those who were sedentary, moderately active or active had similar SDLT scores, though being active was associated with slightly better (lower) SDLT performance. However among participants who were centrally obese the picture was different. Persons who were centrally obese and sedentary showed the worst overall SDLT scores. By contrast persons who were centrally obese but
moderately active or active had SDLT scores similar to non-obese participants. Mean SDLT scores and standard errors for these groups are depicted in Table 2.3.7.

<table>
<thead>
<tr>
<th></th>
<th>Sedentary</th>
<th>Moderately active</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrally obese</td>
<td>6.45 (0.388)</td>
<td>4.37 (0.225)</td>
<td>4.58 (1.76)</td>
</tr>
<tr>
<td>Not centrally obese</td>
<td>4.52 (0.314)</td>
<td>3.89 (0.364)</td>
<td>3.42 (0.181)</td>
</tr>
</tbody>
</table>

**SDLT Model 5. Potential Factors Mediating the Association Between Adiposity and SDLT**

To test the hypothesis that the association between adiposity and cognitive function is mediated by physiological mechanisms potentially linked to cognitive function and adiposity, biomarkers were next added to the model. Building on the behavioral model containing the interaction term, biomarkers were added to the model to determine whether the associations between behavior and cognition was mediated by physiological factors they can affect. Biomarkers added included HbA1c, CRP, IGF-1, systolic blood pressure, and HDL cholesterol. In each adiposity model none of the variables were associated with change in SDLT score, nor did their inclusion, or removal, appreciably alter the direction or magnitude of the associations already found between SDLT and other variables.

**2.3.6 Sub-analysis of the Duration of Obesity**

The following sub-analysis was performed to explore whether duration of exposure to obesity has a significant association with cognitive performance in midlife. It is possible that the chief difference between the results found by observational studies of midlife overweight and cognitive decline, compared to studies of overweight in older adults, is due to the difference in duration of exposure to the harmful effects of obesity. If so, then persons who are obese for longer periods of time during early and mid-adulthood may show worse cognitive performance.
than persons of the same weight who were exposed to a shorter duration of obesity. Although
NHANES-III was a cross-sectional study, it did include some retrospective self-report data on
weight 10 years prior to the interview, as described in the methods and data analysis sections
above.

**Sub-Sample Selection and Characteristics**

To estimate the effects of different lengths of exposure to obesity, participants were
stratified into four groups. Group 1 contained persons who, based on their estimated BMI 10
years ago, were obese at both time points. It is not possible to know if the individual’s weight
fluctuated between those times, but plausible that they remained obese during the entire 10
year period. Group 2 included persons who were not obese 10 years prior to the interview, but
had subsequently gained weight and become obese. Group 3 included participants who
reported obese weights 10 years ago, but were not obese at the time of the interview,
representing probable weight loss at some point in the preceding 10 years. Group 4 included
participants who were not obese at either time point.

Participants aged 20-29 at the time of the NHANES-III interview were excluded from the
sub-sample because 10 years earlier they would not necessarily have reached their full adult
height or weight. After accounting for this, and for missing data in the self-report variable, the
sample available for this sub-analysis included 2363 participants. As shown in Figure 2.3.2,
12.6% were obese at both time points (group 1), 14.8% became obese within the past 10 years
(group 2), only 2% were obese 10 years ago but subsequently lost weight (group 3), and 70.4%
were not obese at either time (group 4). As would be expected, there was a strong correlation
between this variable and BMI at time of interview (R=-0.788, p<0.000).
Figure 2.3.2. Number of participants in each strata of duration variable.

Duration of Obesity and Regression Models of the SRTT

The regression model-building process matched that used for the full sample and described above. For the duration sub-sample, results of SRTT Model 1 demographics only model (including age, education, gender and ethnicity) were similar to those of the larger NHANES sample. Each of these demographic variables was significantly associated with SRTT scores, and the model accounted for 10% of the variance in SRTT.

However SRTT Model 2 showed that, in contrast to the full sample, BMI was not a significant predictor of SRTT in the sub-sample. This may be due to the systematic removal of participants aged 20-29 years from the sub-sample, or it may be due to the loss of power with the smaller sample size. The BMI model accounted for 10.2% of the variance in SRTT, which is actually slightly more than the BMI model was able to account for in the full sample, suggesting that the issue may have been one related to power and sample size, particularly given the very small magnitude of effect for SRTT seen in the full sample model. Running a separate model with just the (dummy coded) “duration of obesity” variable, (BMI removed because of collinearity) produced similar results. The different groups did not show significantly different
scores on the SRTT. This remained true after recoding the “duration” variable to remove the small group of people who reported weight loss, to check whether the small cell size for this group was having an undue effect.

**Duration of Obesity and Regression Models of the SDST**

When including duration of obesity, the **SDST model 1** (the demographics only model) produced results similar to those of the larger NHANES sample described previously for SDST. All of the demographic variables were significantly associated with SDST performance, and the model accounted for 43% of the variance.

As was found in **Model 2** for the full sample for SDST, Model 2 for the sub-sample with duration of obesity showed that BMI was not a significant predictor of SDST in the sub-sample. The model with BMI added did not account for any more variance than the demographics alone (45%). Running a separate model with just the (dummy coded) “duration of obesity” variable produced similar results. Differences in duration were not significantly associated with SDST score. This remained true after recoding the “duration” variable to remove the small group of people who reported weight loss.

**Duration of Obesity and Regression Models of the SDLT**

Results of the demographics only **Model 1** for the SDLT were similar to those of the larger NHANES sample. All demographic variables except gender were significant predictors of SDLT. The model accounted for 27.8% of the variance in SDLT.

However in contrast to the results obtained from the full sample, BMI was not a significant predictor of SDLT in **Model 2** for this sub-sample. This may be due to a loss of power, or to the systematic removal of participants aged 20-29 years from the sub-sample. After adding BMI, the model only accounted for 27.9% of the variance in SDLT. Running a separate model with just the (dummy coded) “duration of obesity” variable (BMI removed) produced similar
results. No level of the duration of obesity variable was associated with SDLT performance. This remained the case after recoding the duration variable to remove the group of people who lost weight over the last 10 years and were no longer considered obese.

2.4 Discussion

Consistent with previous research suggesting a link between midlife obesity and cognitive decline later in life,, greater adiposity in early and mid-adulthood was associated with more difficulty learning and recalling a list of 8 numbers presented repeatedly, after adjusting for age, education, gender and ethnicity. Significantly, the association was most apparent in a test of working memory and attention/concentration - the SDLT cognitive test ((Pavlik et al., 2004; Suhr et al., 2004). Some evidence of a small but statistically significant association between adiposity (BMI, WHR) and simple reaction time was also apparent, however the association disappeared after adding health behaviors to these models. The Symbol Digit Substitution Task (SDST), which tested the speed with which participants matched a single digit with a symbol presented on the screen, and taps attention and psychomotor speed (Pavlik et al., 2004; Suhr et al., 2004; Wechsler, 1981), was not associated with markers of adiposity. This difference suggests that the finding is more than just a spurious result. While learning and memory are not the only cognitive functions that have been linked to excess body weight in epidemiological research (Wolf et al., 2007) they are more commonly implicated than any other domain. Furthermore, animal models of interventions that affect weight and metabolism, such as physical activity, calorie restriction and intermittent fasting demonstrate improvements in learning and memory (Mattson et al., 2003).

Central obesity (WHR) was more closely related to performance on both the SRTT and the SDLT. While both global obesity and central obesity were associated with SDLT test performance, the magnitude of the association between SDLT score and central obesity (WHR)
was greater than that found for either BMI or percent fat mass. Based on these regression results, when holding other things constant, a man with a waist circumference of 40.5 inches and buttock circumference of 45 inches (WHR=0.90) would be predicted to score 0.56 points worse on the SDLT than a man with a waist circumference just half an inch smaller (40.0 inches, WHR=0.89). By contrast, an 180lb man with 26% fat mass would score just 0.035 points worse than a similar man carrying 0.45lbs less fat (26% fat mass). Thus the difference of half an inch in waist circumference is linked to greater differences in SDLT than the gaining of almost half a pound of fat mass. This difference between the measures of adiposity reinforces the value of adding alternate measures of obesity to future research studies. As previously described, studies using BMI as the sole measure of obesity when studying the relationship to cognitive outcomes miss this distinction – and with it valuable information on the effects of adiposity on neurocognitive health. It is also consistent with epidemiological studies described in Study 1 found that midlife central obesity was more often linked to cognitive decline and dementia than late life central obesity. The reasons for a link in midlife certainly warrant further investigation. Intervention studies with the potential to draw causal inferences would be particularly valuable in this regard.

Different measures of adiposity also showed different associations with health behaviors. Percentage fat mass and WHR remained significant predictors of SDLT performance after controlling for health-related behaviors, but this was not true for BMI. Quality of diet and being a former smoker attenuated the association between BMI and SDLT performance.

Although the magnitude of the associations, and the differences between the measures of adiposity, were small they are potentially significant. The association was found in adults aged 20-59 years, after controlling for age. This is consistent with longitudinal studies that found an association between obesity in midlife and later cognitive decline (Cournot et al., 2006a;
Furthermore, unlike research with older adults, the cross-sectional association in midlife is unlikely to be confounded by undiagnosed dementia. Although it is not possible to conclude from these cross-sectional data that a gain in waist circumference would lead to worse SDLT scores, a causal role for obesity in cognitive decline could have significant cumulative effects over a prolonged period of time. This would also be consistent with the prior research reporting an association between central obesity in midlife and cognitive decline or dementia later in life (West & Haan, 2009).

The association between duration of obesity and cognitive function could not be determined from the data obtained. This was at least partly due to the sample and power available, or possibly inaccuracies of 10 year recall in weight. In the sub-sample of participants aged 30-59 who had self-report data on their weight 10 years ago, and who met all other inclusion criteria, the regular adiposity models did not show the significant effects that were found in the full sample. It is therefore not surprising that no association was observed between groups likely exposed to differing duration of obesity. However this null finding also suggests that if there is an effect of duration of obesity the effect size is not likely to be dramatically large in this age group. Further research on this is needed, and future longitudinal studies would do well to include repeated measures of fluctuations in weight over time to provide a more accurate estimate of the effects of duration of obesity on cognitive function in midlife and beyond.

It should be noted that health-related behaviors had some independent associations with SDLT performance. As previously noted, it is possible that poor quality diet or sedentary lifestyle, are the real culprit in the association between obesity and cognitive decline, rather than the physiological effects of obesity itself. However in this study we did not find support for the idea that quality of diet was worse among persons who were obese. Quality of diet,
measured by the Healthy Eating Index (HEI: range 1 – 100, mean of 62.39 in this sample), did not differ significantly between BMI groups, and the correlation with this and other measures of adiposity was low. Despite this, quality of diet was significantly associated with SDLT performance, independent of weight. The magnitude of the improvement in SDLT score was small. The improvement in SDLT associated with a 1 point improvement in HEI (-0.017 SDLT points) was almost half of that found for BMI or percent fat, and more than 3 times smaller than that associated with WHR. No interaction between HEI and any measure of adiposity was found. So while quality of diet may have independent associations with cognition, it did not appear to moderate the association with obesity in this study.

Smoking status was also related to cognitive performance. Interestingly, being a former smoker was significantly associated with better SDLT score relative to persons who never smoked. The reason for this finding is unclear, however it could reflect a composition effect – persons who succeed in quitting smoking may differ from those who have not quit, or from those who never started smoking. Longitudinal or intervention studies with baseline pre-smoking measures of cognitive function and repeated measures comparisons would be useful future approaches to tell the story.

Physical activity is another health behavior that affects obesity. Unlike the other health-related behaviors measured, PA moderated the association between central obesity and SDLT performance. Among persons who were not centrally obese, more regular physical activity was associated with better SDLT scores. As predicted, persons who were centrally obese but active had better cognitive performance than persons who were centrally obese but sedentary, and being moderately active was associated with the best cognitive scores. Hence there was a significant interaction between PA and adiposity on SDLT performance. This is consistent with the reports of beneficial effects of physical activity on cognitive function made elsewhere (Baker
et al., 2010; Buchman et al., 2012; Erickson et al., 2010; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Voss et al., 2013). It is possible that the benefits of physical activity on cognition are independent of weight or weight loss, making this a potential candidate for interventions to promote neurocognitive health across the population. Further research is needed to determine the efficacy of interventions in promoting neurocognitive health however, for this cross-sectional association could be an artifact of composition effects (e.g. persons who are obese and active may represent a rather unique segment of the population), or other factors not measured here.

In this study we did not find sufficient evidence to indicate a role for HbA$_1$c, CRP, IGF-1, systolic blood pressure or HDL cholesterol in mediating the association between adiposity and cognitive function. Adding any of these potential mechanisms to the model either individually or in combination did not have a significant effect on the association, nor were any of these measures significant predictors of cognitive function. This contrasts with some other studies finding an association between glucose regulation, inflammation, IGF-1, hypertension and dyslipidemia and cognitive function (Carro, Trejo, Busiguina, & Torres-Aleman, 2001). However results of the prior research have been mixed. Many possible explanations for the null findings here are possible. They may be at least partially due to the limitations on sample size that some of these variables created, as some were only measured in a sub-sample (e.g. IGF-1). Alternatively it may be that the action of these factors is not independent of adiposity, particularly central adiposity, so that a model already adjusting for adiposity will not show an effect without interaction terms. Addition of such interaction terms to this study would impose serious sample size limitations and the difficulty of interpreting interactions between continuous variables should not be overlooked.
While numerous longitudinal studies of the association between adiposity and cognitive decline and dementia have been conducted, relatively few of these have assessed central obesity, and even fewer have assessed the moderating role of health behaviors or potential mediation of the association by physiological factors shown to affect cognitive function. These factors should be included in future longitudinal studies of cognitive aging. New intervention studies to assess the effects of weight loss, or change in obesity-related behaviors, should also incorporate these factors into their designs.

Though limited by a cross-sectional study design, self-report measures of behavior and a small number of cognitive tests, the results of this study are consistent with emerging evidence that modifiable factors in mid-adulthood are associated with cognitive function. Obesity-related deficits could be apparent decades before dementia would be likely to occur. While the population in this study could not be considered pre-clinical, the finding of an association between obesity and cognitive function in midlife is worth noting. Not only was weight associated with cognitive test performance, but physical activity moderated the association between central obesity and minor cognitive deficits in the general population in early and mid-adulthood. Further research is needed to determine whether weight loss interventions, or other interventions that affect the health risks of obesity, can significantly improve cognitive function in persons who are obese.
3. **Interventions**

3.1 **Introduction**

Taken together the observational studies suggest a link between obesity and risk of cognitive decline or dementia. Consistent with this, intervention studies present evidence that reducing weight can have beneficial effects on cognitive function.

If obesity contributes to cognitive decline and dementia, then interventions that reduce obesity, or moderate the health risks that it imposes, could improve cognitive function in obese adults. Such interventions could have significant public health implications, providing both a means for improving neurocognitive health in the short term and supporting healthy cognitive aging among the increasingly overweight and obese population. Interventions could also provide a useful opportunity to explore causal mechanisms relevant to the understanding of dementia etiology.

Increasing physical activity and altering dietary intake are well-known approaches to weight management. These affect not only daily energy balance, but also modulate some of the mechanisms implicated in the pathology of obesity and dementia. The purpose of this paper is to discuss the evidence that physical activity and dietary interventions can affect the risk of cognitive decline and dementia among adults who are overweight or obese.

3.2 **Physical Activity Interventions**

Regular physical activity (PA) provides well-recognized reductions in risk for cardiovascular disease, Type 2 diabetes mellitus, metabolic syndrome, osteoporosis and depression (Bassey, 2000; Byberg, Zethelius, McKeigue, & Lithell, 2001; Wannamethee, Shaper, & Alberti, 2000). It may also decrease stress and depression (Brown et al., 2010; Brown, Varghese, & McEwen, 2004; Gamble, Ormerod, & Frenneaux, 2008; Strawbridge, Deleger, Roberts, & Kaplan, 2002; Trivedi, Greer, Grannemann, Chambliss, & Jordan, 2006). Among older
adults PA can help to maintain strength and physical function and hence independence and the benefits of an engaged lifestyle (Aufderm, 2013). Older adults who regularly participate in endurance, balance and resistance training can experience benefits that include improved muscle mass, arterial compliance, energy, metabolism, cardiovascular fitness, muscle strength, overall functional capacity (Lemura, von Duvillard, & Mookerjee, 2000). In addition to the physical benefits, exercise may also increase self-confidence (Lindwall & Hassmen, 2006).

3.2.1 Animal Studies of Physical Activity

Numerous studies from rats, mice and non-human primates show that PA can have a significant impact on cognitive function and brain health. Regular PA is widely shown to improve learning and memory (Alaei, Moloudi, Sarkaki, Azizi-Malekabadi, & Hanninen, 2007; Cotman & Berchtold, 2002; Molteni et al., 2004; Ploughman, 2008; Radak et al., 2001; van Praag, Shubert, Zhao, & Gage, 2005). For example Khabour (Khabour, Alzoubi, Alomari, & Alzubi, 2010) showed that 6 weeks of voluntary exercise significantly increased short-term, medium term and long-term spatial memory formation and increased BDNF in hippocampus twofold in male Wistar rats. PA can also lower the risk of cognitive impairment (Cotman & Berchtold, 2002) and reduce the effects of brain aging (Laurin et al., 2001). Furthermore, PA can enhance resilience against damage caused by neurodegenerative diseases (Tillerson, Caudle, Reveron, & Miller, 2003; Wu et al., 2011), and may mediate recovery of function after brain injury (Bohannon, 1993; Grealy, Johnson, & Rushton, 1999; Naylor et al., 2008). For example Gobbo and O’Mara (Gobbo & O’Mara, 2005), found that PA before administration of Kainic acid (causing neuronal death by apoptosis and necrosis) improved functional performance on the Morris water maze and object exploration tasks and increased BDNF in the dentate gyrus relative to controls. Similarly Wu (Wu et al., 2011) found that 4 weeks of PA prior to injection of LPS (which induces loss of dopaminergic neurons and decreases BDNF in the substantia nigra of a mouse model of
Parkinson’s disease), completely prevented LPS induced loss of neurons and restored BDNF signaling. Blocking BDNF using receptor TrkB antagonist removed the PA induced protection against LPS-induced neuronal loss. Thus animal studies suggest that PA can have significant neuroprotective effects.

3.2.2 Human Studies of Physical Activity

Observational Studies

Most observational studies of PA among humans use self-reported PA, often retrospective reports, while few use objective measures of PA (Spencer & Karzeski, ref). This inevitable introduces unwanted error in their results, which should be treated with appropriate caution. With this in mind we consider the evidence for an association between PA and neurocognitive health.

Association with risk of dementia: Numerous observational studies report that persons who engage in regular PA show decreased risk of dementia, including AD. For example, Scarmeas and colleagues (Scarmeas, Levy, Tang, Manly, & Stern, 2001) found that leisure-time activity was associated with decreased risk of dementia in older adults. Similarly, Laurin and colleagues (Laurin et al., 2001) reported that higher levels of PA among high functioning older adults (>65) were associated with lower rates of cognitive decline and dementia, including AD, 5 years later. Consistent with this, Abbot et al (Abbott et al., 2004) found an association between distances walked each day and probability of developing AD up to 8 years later among men aged 71-93 years. While the preceding studies used self-report measures of PA, similar results were reported by Buchman (2012), who used actigraphs to provide objective measures of PA to assess incidence of AD. After an average follow-up of about 4 years, PA at baseline was associated with decreased risk of AD (HR 0.477, 95% CI: 0.273-0.832), and rate of global
cognitive decline, even after controlling for self-reported physical, social, or cognitive activities, depressive symptoms, motor function, chronic health conditions and APOE genotype.

Some observational studies find no evidence of a link between PA and dementia risk (Fabrigoule et al., 1995), however several systematic reviews and meta-analyses of prospective studies in on PA, including the NIH consensus report on preventing cognitive decline and dementia (Plassman et al., 2010) have concluded that observational studies suggest that increased physical activity is associated with decreased dementia risk. This includes evidence that PA in midlife is associated with significantly reduced risk of MCI or dementia later in life (Skog, 2011).

**Association With Cognitive Function or Risk of Cognitive Decline:** As with the studies on dementia, a mounting body of evidence links regular PA to lower rates of cognitive decline (Fratiglioni et al., 2004). A number of cross-sectional studies show better neurocognitive function in persons who are physically active (Smith et al., 2010b). Prospective studies show similar results. In a study of 5925 community-dwelling women, Yaffe et al (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001) found that women who were more active experienced less cognitive decline over the following 6-8 years, after adjusting for age, education, health status, depression, stroke, diabetes, hypertension, smoking, and estrogen use. Richards, Hardy and Wadsworth (Richards, Hardy, & Wadsworth, 2003) found a similar association in midlife. Among 1919 adults aged 36 at baseline and followed up to ages 43-53, PA was associated with better memory performance. While it is likely that many different aspects of PA contribute to the association, Barnes et al (Barnes, Yaffe, Satariano, & Tager, 2003) found that aerobic fitness, assessed by V02 peak, predicted higher cognitive performance 6 years later. Other studies have found no association between PA and cognitive function. For example Holtsch et al (1999) found
no association between PA and cognitive function after a 6 year follow-up with in adults aged 55 – 86 years.

**Intervention Studies**

Studies of the effects of PA interventions on human cognition or dementia risk have likewise produced mixed results, possibly reflecting the wide range of interventions, populations and cognitive outcome measures used (Kramer, Colcombe, McAuley, Scalf, & Erickson, 2005). The variety is easily observed on inspection of the research in this area. For example Liu-Liu-Ambrose et al. (2010) found that resistance training improved executive function by more than 10%. after conducting a 12mo RCT among community-dwelling women aged 65-75 years. (Baker et al., 2010) reported sex-specific benefits of a 6-month aerobic PA intervention on executive function, fasting insulin, cortisol and BDNF (improved in women but not men) after a well-controlled RCT randomizing 33 adults aged 33-85 years to either 6-months of supervised aerobic PA or 6-months supervised stretching control. In another study, Ruscheweyh et al (Ruscheweyh et al., 2011) found that increased aerobic PA was associated with increased memory increased gray matter volume in the prefrontal and cingulate cortex, and a trend for increased BDNF among 62 healthy older adults. By contrast, Erickson and colleagues (Erickson et al., 2011) found that aerobic exercise training did not alter spatial memory relative to stretching control, but did increase the size of the anterior hippocampus as well as circulating BDNF.

Given the mounting evidence from observational studies, and the varied intervention studies, a number of recent systematic reviews and meta-analyses have investigated the evidence that PA interventions could protect cognitive function and prevent dementia. In a review of aerobic PA interventions, Smith (Smith et al., 2010b) reported that aerobic PA was associated with modest improvements in memory relative to controls with effects of similar magnitude across the 16 studies. However intensity and duration of PA did not appear to
moderate the effect. Another meta-analyses concluded that RCTs show a clear effect of aerobic PA on varied cognitive function (Kramer et al., 2005). A meta-analysis by Heyn, Abreu, and Ottenbacher (2004) found an effect of PA training on the cognitive function of cognitively impaired older adults and people with dementia, and these results were echoed in another more recent review concluding that RCTs among persons with MCI or dementia show that 6-12 months of PA improve cognitive scores relative to sedentary controls (Skog, 2011). Despite the results of these reviews, others with more stringent entry criteria and quality ratings have drawn different conclusions. A Cochrane review of the effects of PA and enhanced fitness on cognitive function in persons without known cognitive impairment (Aufderm et al, 2008), found that the data are currently insufficient to draw conclusions in this area. A systematic review by Snowden et al (Snowden et al., 2011) drew a similar conclusion, determining that no studies showed really good quality overall. Limitations of the studies included small sample size, non-randomized and quasi-experimental study designs, and widespread absence of intention-to-treat analyses. The recent NIH consensus report on preventing cognitive decline and dementia reported that observational studies suggest a link between reduced PA and cognitive decline, but found only 1 intervention study that met the quality standards for inclusion. This study (Lautenschlager & Almeida, 2006)2008) showed that among 138 adults aged >50 years with subjective memory problems but not dementia, a home-based 6-month PA intervention produced modest but significant improvements in scores on the Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) 12-months later.

Differences between the results of observational studies and intervention studies in this area may reflect not only the difficulty of constructing and funding large, well-controlled PA trials, but also the fact that observational studies have typically examined much longer time spans than intervention studies (Snowden et al., 2011). Consistent with links between PA in
midlife and cognitive function in later life, it may be that the benefits of PA are gradually cumulative over time, and that regular exposure over a prolonged period of time is an important. Alternatively it is possible that the association between PA and cognitive function is simply an artifact of underlying differences between people who are likely to exercise and people who do not. However, as with obesity, there are plausible mechanisms that could mediate an effect of PA on neurocognitive health.

3.2.3 Potential Mechanisms for an Effect of Physical Activity

Animal research has provided valuable insights into the actions of PA on the brain (Aufderm et al, 2005). Physical activity can promote long-term potentiation (LTP), a physiological process believed to be the cellular correlate of learning and memory in the hippocampus (O’Callaghan, Ohle, & Kelly, 2007). It can also produce numerous neuroprotective changes, including enhanced neurogenesis (Aberg, Perlmann, Olson, & Brene, 2008; van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Kempermann, & Gage, 1999) and increased synaptic plasticity (Farmer et al., 2004; O’Callaghan et al., 2007). In a mouse model of AD (TgCRND8), 5 months of voluntary PA enhanced learning and memory and decreased amyloid burden in the frontal cortex and hippocampus, possibly by altering the processing of the amyloid precursor protein (Adlard, Perreau, Pop, & Cotman, 2005).

Physical activity can also affect factors thought to be involved in neuronal health and amyloid clearance. For example episodes of PA can increase IGF-1 (Carro et al., 2001; Kohman, DeYoung, Bhattacharya, Peterson, & Rhodes, 2012), which in turn can induce β-amyloid clearance (Carro et al., 2002). In addition, exercise can increase BDNF in brain areas such as the hippocampus (Vaynman & Gomez-Pinilla, 2006; Vaynman, Ying, Yin, & Gomez-Pinilla, 2006). As previously described, BDNF is involved in synaptic plasticity, neurogenesis and neuronal survival (Cotman & Berchtold, 2002; Mattson, Maudsley, & Martin, 2004b; Shirayama, Chen, Nakagawa,
Russell, & Duman, 2002; Zhang & Pardridge, 2006). A number of animal studies suggest that the beneficial effects of PA on cognitive function and neural health may be mediated by BDNF (Gobbo & O’Mara, 2005; Khabour et al., 2010), and that these effects are blocked by blocking the BDNF receptor (Dishman et al., 2006; Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004; Vaynman & Gomez-Pinilla, 2006). Physical activity can also beneficially affect other pathways implicated in neurocognitive health, including a “stress-buffering” effect (Kramer, Fleshner, Maier, Lyons and Raskind, 2011) that could be an important counter-balance to the HPA axis dysregulation sometimes reported with advancing age (Kramer, Erickson, & Colcombe, 2006).

Research among humans indicates that PA can have effects not only on cardiovascular fitness and BDNF (Baker et al., 2010; Erickson et al., 2011; McAuley, Kramer, & Colcombe, 2004) but also brain structure and function (Colcombe & Kramer, 2003; Colcombe et al., 2005). For example an aerobic PA interventions as short as 6 months has been shown to increase brain volume in areas such as the anterior cingulate, middle frontal gyrus, and superior temporal lobe (Colcombe et al., 2004), and improve functional performance (Colcombe et al., 2005).

3.3 Study 3: Calorie Restriction Interventions

3.3.1 Introduction

Caloric restriction (CR) is the most widely studied form of dietary restriction in animal models, and corresponds most closely to the dieting often used for weight loss among humans. Caloric restriction can increase median lifespan in rodents, flies, yeast and non-human primates (Heilbronn & Ravussin, 2003) and has many beneficial effects on markers of aging and vulnerability to age-related disease (Berner & Stern, 2004; Mager et al., 2006; Mattson et al., 2003; Roth, Ingram, & Lane, 2001; ROTH, LANE, & INGRAM, 2005). Behaviorally, CR increases
exploration and physical activity in rodents (Martin et al., 2007b). Furthermore, mice maintained on 40% CR from time of weaning do not exhibit the deficits in motor coordination and spatial learning that are seen in control mice fed ad libitum (Ingram et al., 2001). Similarly, life-long CR prevents age-related deficits in performance on learning and memory tasks such as the radial arm maze and Morris water maze (Martin et al., 2007b; Stewart, Mitchell, & Kalant, 1989). Cognitive and behavioral effects have also been reported when CR was initiated at midlife (Means, Higgins, & Fernandez, 1993).

At a neural level, CR reduces age-related deficits in long-term potentiation (LTP), a process believed to be the cellular correlate of learning and memory, in the hippocampus. CR has also been shown to improve synaptic plasticity and dendritic branching (Mattson, Maudsley, & Martin, 2004a; Stranahan et al., 2009a), as well as to increase resistance to degeneration after excitotoxic injury in a rat model relevant to the pathogenesis of epilepsy and AD (Bruce-Keller, Umberger, McFall, & Mattson, 1999; Duan et al., 2001a; Zhu, Guo, & Mattson, 1999). This neuroprotection corresponded with preserved learning and memory. Neurons in brain regions involved in learning and memory, such as the hippocampus and prefrontal cortex, are affected in AD (Ray et al. 1998) and are among the areas protected against injury and degeneration by CR.

While CR has clear neuroprotective effects in animals, its effects on human cognitive function are less clear. Much of the evidence in animal studies has come from CR interventions that began shortly after weaning or in early adulthood, in rodents that were not previously overweight. As such they neither illustrate the effects of weight loss and it is difficult to determine whether effects result from exposure during critical periods in early in life. The effects of weight loss by calorie restriction on human cognitive function are not yet fully understood. As previously discussed, epidemiological evidence suggests that overweight and
obesity in midlife increase risk of cognitive decline and dementia later in life, but numerous studies also link weight loss to cognitive decline and dementia. This finding was more frequent among older adults and may reflect early dementia pathophysiology in these observational studies. Nonetheless, the effects of weight loss interventions on human cognition warrant further investigation.

### 3.3.2 Methods

**Literature Search Terms and Study Inclusion Criteria**

English-language articles focused on weight or adiposity and cognition or dementia outcomes were identified using MEDLINE and PsycINFO. The following search terms were used in various combinations: dementia, Alzheimer’s disease, cognition disorders, cognitive decline, cognitive impairment, cognition, cognitive function, and cognitive health, as well as obesity, overweight, weight, fat, adiposity, central obesity, visceral obesity, visceral adiposity, waist-hip ratio, and waist circumference. All relevant articles published up until January 30th, 2013 and retrievable by university library search or interlibrary loan were considered for this systematic review. Reference lists of all potentially eligible articles were reviewed to ensure inclusion of all relevant literature.

To be included in this review, the articles had to meet the following eligibility criteria: empirical intervention studies assessing adult cognitive function that are available via university libraries or interlibrary loan, written in English, and included the weight/adiposity and dementia/cognition related search terms above within the title, abstract, and/or keywords. Interventions in childhood or adolescence were considered only if they included adult cognitive outcomes. Interventions to change the weight of a population that already had dementia at baseline were excluded. Similarly interventions to improve the health outcomes for other cognitively impaired persons with an existing medical or psychiatric diagnosis known to cause
cognitive impairment, such as developmental disability, schizophrenia, bipolar disorder or traumatic brain injury, were excluded. Studies with a specific focus on eating disordered populations were also excluded, as were other studies focused on specific medical or psychiatric populations. Dissertations, reviews, opinions, theoretical papers or editorials were excluded from this review.

Article Selection and Abstraction

A three-step process guided assessment and selection of articles. First, the study author reviewed the titles and abstracts of all potential articles retrieved by the search terms, identifying the set of article abstracts that potentially matched the eligibility criteria. Second, the study author reviewed in-depth the abstracts and full articles for studies whose abstracts passed the first review for inclusion. Information from the full articles was entered into summary tables. From this set the author identified the set of full articles which matched the eligibility criteria below. Finally, reference lists of eligible articles were reviewed for additional relevant articles to potentially include. These articles were also assessed for eligibility through a two step process.
3.3.3 Results

Number of Articles Included in Review

A total of 4320 articles were identified using the search terms. Of these articles, 4085 were excluded after a preliminary review of title and/or abstract because they were not relevant or did not meet the inclusion criteria (e.g. topic was relevant but the article was an editorial). The remaining 235 full articles were then reviewed and abstracted by the study author. Of these articles, 16 intervention studies were considered eligible after more thorough review, and were therefore included in this study. Included articles were then categorized by whether
their results showed beneficial effects of weight loss interventions on adult cognitive function, no effect, or detrimental effects. A flow chart of the sorting and inclusion process can be seen in Figure 3.3.1.

**Beneficial Effects**

Among the 16 intervention studies included in this review, 10 showed beneficial effects of weight loss diets on cognitive function. Six of these studies showed beneficial effects on memory recall (Gunstad, 2011; Halyburton, 2007; Kretsch, 1997; Krikorian, 2012; Smith, 2010; Witte, 2009). One of these interventions reported the results of bariatric surgery (Gunstad, 2011. The other interventions ranged from 6 weeks to 4 months and most involved 30-50% caloric restriction.

Other cognitive domains that showed beneficial changes after interventions included working memory (Brinkworth, 2009), reaction time (Buffenstein, 1999; Kretsch, 1997), speed of processing (Brinkworth, 2009; Halyburton, 2007; Siervo, 2012; Smith, 2010), accuracy (Bryan, 2000; Buffenstein, 1999), and executive function (Siervo, 2012; Smith, 2010).

**No Effects or Detrimental Effects**

Of the 16 intervention studies exploring the effects of dieting for weight loss on adult cognitive function, 6 reported either no effect on cognitive function or adverse effects. These studies tended to have smaller sample sizes than the studies showing beneficial effects, tended to be of shorter duration and may have involved a smaller degree of calorie restriction. The interventions employed a similar range of cognitive tests to the other studies that showed benefits, including tests of short-term and long-term memory.
Table 3.3.1. Intervention studies with beneficial effects on cognition.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Participants</th>
<th>Intervention</th>
<th>Cognitive measures</th>
<th>Weight measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Brinkworth, Buckley, Noakes, Clifton, &amp; Wilson, 2009)</td>
<td>N=106, Age: 24 - 64 Mean 50.0 [0.8]. Other: central obesity + at least 1 MetS factor.</td>
<td>Duration: 1 year Randomized: yes Groups: 1) very low-carb, high-fat (LC) 2) a high-carb, low-fat (LF) diet for 1 year.</td>
<td>Digit span backward (DSB), inspection time</td>
<td>Weight</td>
<td>Each group achieved similar weight loss, with no significant difference between the diets. Working memory improved by week 8 and remained stable at 1 year (P &lt; .001). Speed of processing improved at week 8 but rebounded to original levels by week 52. Significant inverse association between change in working memory and change in fasting insulin.</td>
</tr>
<tr>
<td>(Bryan &amp; Tiggemann, 2001)</td>
<td>N=63 Age: 30-50 Other: overweight women</td>
<td>Duration: 12 weeks Groups: 1) 42 Ss weight reduction diet (15% fat, 2) 21 usual diet controls</td>
<td>Digit Symbol-Coding subtest of the of WAIS III,Trail Making Test Part A &amp; B, Stroop test, Self-Ordered Pointing Task, Digit Span-Backwards subtest of WAIS III, Rey Auditory-Verbal Learning Test [RAVLT], verbal ability.</td>
<td>BMI Weight</td>
<td>Being on the diet made participants less susceptible to interference effects and more accurate in their recall. No other measure of cognitive performance was affected by being on the diet.</td>
</tr>
<tr>
<td>(Buffenstein, Karklin, &amp; Driver, 2000)</td>
<td>N=9 Age: 20-36 Other: overweight university students, women</td>
<td>Duration: 4 weeks Randomized: no Groups: Restrict food &amp; beverage intake to 800 kcal/day.</td>
<td>2 different visual hand-eye coordination reaction tests</td>
<td>BMI</td>
<td>Motor performance reaction time and accuracy improved. Urinary ketones not associated with deterioration in cognitive performance. Mood, concentration, temperature sensitivity, appetite, and sleep quality using visual analogue scales, were not significantly altered.</td>
</tr>
</tbody>
</table>
### Table 3.3.1. Intervention studies with beneficial effects on cognition.

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>(Gunstad et al., 2011)</td>
<td>N= 150 Age: 20 - 70 Other: obese</td>
<td>Duration: na Randomized: No Groups: 1) Bariatric Surgery 2) control</td>
<td>Integneuro test battery.</td>
<td>Weight</td>
<td>Surgery patients had improved memory performance at 12 week follow-up whereas obese controls actually declined.</td>
</tr>
<tr>
<td>(Halyburton et al., 2007)</td>
<td>N=93 Age: 24-64 Other: overweight or obese</td>
<td>Duration: 8 weeks Randomized: yes Groups: 1) 30% deficit LCHF 2) 30% deficit HCLF</td>
<td>Digit span backwards (DSB) and inspection time (IT) tests.</td>
<td>Weight; checked at baseline and every 2 weeks</td>
<td>LCHF diet group had greater weight loss than the HCLF diet group. DSB test scores increased in both groups(P&lt;0.001 for time effect). The difference between the groups was not significant (P= 0.67). Speed of processing improved in both treatment groups during the intervention but with a significant effect of diet; the HCLF diet promoted greater improvements in speed of processing than did the LCHF diet.</td>
</tr>
<tr>
<td>(Kretsch, Green, Fong, Elliman, &amp; Johnson, 1997)</td>
<td>N= 25 Age: 23-42 Other: healthy, obese premenopausal women</td>
<td>Duration: 21 weeks Randomized: Groups: 1) 50% caloric restriction for 15 weeks.</td>
<td>Bakan vigilance task, word recall task, simple reaction time,2 finger tapping task, Ericksen effect.</td>
<td>BMI, body composition (TOBEC)</td>
<td>Dieting women lost 12.3 += 5.5 kg of body weight. CR significantly improved word recall by 24%. CR significantly slowed simple reaction time. This did not readily reverse upon restoration of sufficient calories to maintain body weight. No effect for obese women on sustained attention and finger tapping.</td>
</tr>
</tbody>
</table>
Table 3.3.1. Intervention studies with beneficial effects on cognition.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Participants</th>
<th>Intervention</th>
<th>Cognitive measures</th>
<th>Weight measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Krikorian et al., 2012)</td>
<td>N=23 Age: mean 70.1 Other: older adults with MCI</td>
<td><strong>Duration:</strong> 6 weeks <strong>Randomized:</strong> yes <strong>Groups:</strong> 1) 50% deficit high carb. (50% of calories) 2) very low carb diet</td>
<td>Verbal memory performance, Trail Making Test Part B, Verbal Paired Associate Learning Test (V-PAL), Geriatric Depression Scale (GDS)</td>
<td>Weight, waist circumference, fasting glucose, fasting insulin, urinary ketones</td>
<td>Very low carbohydrate diet led to improved verbal memory as well as reductions in weight, waist circumference, improved fasting insulin &amp; glucose. Ketone levels positively correlated with memory performance.</td>
</tr>
<tr>
<td>(Siervo et al., 2012)</td>
<td>N=50 Age: Other: obese</td>
<td><strong>Duration:</strong> Until subjects lost 8-10% body weight <strong>Randomized:</strong> No <strong>Groups:</strong></td>
<td>Mini-Mental State Examination (MMSE), Short Portable Mental Status questionnaire (SPMSQ), Trail-Making Test (TMT) A &amp; B</td>
<td>Weight, height, WHR, FM, FFM,</td>
<td>MMSE and TMT-B scores improved significantly after weight loss in older obese participants, The middle-aged group showed improvement in speed processing (TMT-A and B).</td>
</tr>
<tr>
<td>(Smith et al., 2010a)</td>
<td>N=124 Age: Other: high blood pressure, overweight to obese</td>
<td><strong>Duration:</strong> 4 months <strong>Randomized:</strong> yes <strong>Groups:</strong> 1) DASH diet alone 2) DASH + behavioral weight management (WM) including exercise and CR Control (usual diet)</td>
<td>Trail Making Test B &amp; A, Verbal Paired Associates, Stroop Interference Test, Controlled Oral Word Assoc. Test, Verbal fluency Test, Digit Span, Ruff 2 and 7 Test, Digit Symbol Substitution Test</td>
<td>BMI,</td>
<td>DASH diet combined with a behavioral weight management program (DASH + WM) showed greater improvements in executive function-memory-learning and psychomotor speed, compared with the usual diet control. Neurocognitive improvements appeared to be mediated by increased aerobic fitness and weight loss.</td>
</tr>
</tbody>
</table>
### Table 3.3.1. Intervention studies with beneficial effects on cognition.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Participants</th>
<th>Intervention</th>
<th>Cognitive measures</th>
<th>Weight measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Witte, Fobker, Gellner, Knecht, &amp; Floel, 2009)</td>
<td>N= 50 Age: mean 60.5 Other: 50 normal to overweight elderly subjects</td>
<td>Duration: 3 months Randomized: Groups: 1) CR - 30% reduction 2) 20% increase UFAs 3) Control</td>
<td>German Rey Auditory Verbal Learning Task (AVLT), Trail Making Tests (TMT) A &amp; B, forward and backward Digit Span</td>
<td>Weight, height, BMI, WHR,</td>
<td>Significant increase in verbal memory scores after caloric restriction diet (mean 20%) correlated with decreased fasting insulin and high CRP. Significant weight loss in the CR group. BDNF unchanged.</td>
</tr>
</tbody>
</table>
### Table 3.3.2. Intervention studies with no effects, or adverse effects, on cognition.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Participants</th>
<th>Intervention</th>
<th>Cognitive measures</th>
<th>Weight measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Cheatham et al., 2009)</td>
<td>N= 42 Age: 35 ± 5 Other: overweight</td>
<td>Duration: Randomized: yes Groups: 1) High glycemic load (HG) &amp; 10% CR 2) High glycemic load (HG) &amp; 30% CR 3) low glycemic load (LG) &amp; 10% CR 4) low glycemic load (LG) &amp; 10% CR</td>
<td>Simple reaction time, vigilance, learning, short-term memory and attention, and language-based logical reasoning.</td>
<td>BMI, weight</td>
<td>No significant change over time or vs. weight change in any cognitive performance values.</td>
</tr>
<tr>
<td>(Choma, Sforzo, &amp; Keller, 1998)</td>
<td>N= 29 Age: college age Other: wrestlers</td>
<td>Duration: Randomized: Groups: 1) Rapid weight loss (RWL) 2) Control (maintained normal body weight and diet)</td>
<td>Letter cancellation, a test of visual attention and visuomotor skills, digit symbol and digit span, tests of attention and short term memory, Trail Making A and B, story recall.</td>
<td>Weight,</td>
<td>After RWL, wrestlers scored significantly lower on digit span and story recall tests, than controls. RWL did not affect performance on tasks demanding attention, visual acuity, or visuomotor skills.</td>
</tr>
<tr>
<td>(Green, Elliman, &amp; Kretsch, 2005)</td>
<td>N= 56 Age: 20-45 Other: overweight women</td>
<td>Duration: Randomized: Groups: 1) commercially available weight loss group; 2) diet without any group support using any CR, LC, or LF diet; 3) non-dieting controls</td>
<td>Bakan Vigilance task, Simple reaction time, 2-finger tapping performance, verbal recall, mental rotation task.</td>
<td>Weight, BMI, % body fat</td>
<td>Both groups lost roughly the same body mass. Unsupported dieters lost more body fat. No differences in performance between groups. Unsupported dieting was associated with impaired cognitive function in the early stages.</td>
</tr>
<tr>
<td>(Guldstrand et al., 2003)</td>
<td>N= 8 Age: 26-55 Other: severely obese non-diabetic</td>
<td>Duration: na Randomized: No Groups: Vertical banded gastroplasty (VBG),</td>
<td>Perceptual maze test (PMT)</td>
<td>Weight</td>
<td>After weight loss subjects used a more speed, rather than accuracy, preferring cognitive strategy.</td>
</tr>
<tr>
<td>First author (year)</td>
<td>Participants</td>
<td>Intervention</td>
<td>Cognitive measures</td>
<td>Weight measures</td>
<td>Results</td>
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<tr>
<td>(Martin et al., 2007b)</td>
<td>N= 48</td>
<td>Duration: 6 months&lt;br&gt;Randomized: yes&lt;br&gt;Groups:&lt;br&gt;1) control (weight maintenance)&lt;br&gt;2) CR (25% restriction)&lt;br&gt;3) CR + structured exercise (12.5% restriction + 12.5% increased energy expenditure)&lt;br&gt;4) low-cal diet (890 kcal/d until 15% weight loss, then weight maintenance).</td>
<td>Rey Auditory and Verbal Learning Test (RAVLT), Auditory Consonant Trigram (ACT), Benton Visual Retention Test (BVRT), Conners’ Continuous Performance Test-II (CPT-II)</td>
<td>Weight</td>
<td>No consistent pattern of verbal memory, visual retention memory, or attention &amp; concentration deficits.</td>
</tr>
<tr>
<td>(Wing, Vazquez, &amp; Ryan, 1995)</td>
<td>N= 21</td>
<td>Duration: 28 days&lt;br&gt;Randomized: yes&lt;br&gt;Groups:&lt;br&gt;1) ketogenic liquid formula&lt;br&gt;2) non-ketogenic liquid formula very low energy diet</td>
<td>Trail making task</td>
<td>Weight</td>
<td>Weight losses were comparable on the two diets (mean = 8.1 kg). Attention was not affected by diet. Ketogenic diet adversely affected the trail making task.</td>
</tr>
</tbody>
</table>
3.3.4 Discussion

The existing empirical literature on calorie restriction interventions or dieting for weight loss in humans (n=16 studies) reveals a mixture of results that show a beneficial effect of CR or weight loss dieting on adult cognitive function, and other studies that find no effect or adverse effects. However more studies found beneficial effects (n=10) than found null or adverse effects (n=6). Those reporting beneficial effects tended to have larger sample sizes, longer durations and involved more energy restriction.

Significant beneficial effects on memory were demonstrated for 6 interventions. Although one of these interventions involved bariatric surgery (Gunstad, 2010), the other 5 interventions involved calorie restriction of 30%-50% energy restriction and ranged in duration from 6 weeks – 4 months (Halyburton et al., 2007; Kretsch et al., 1997; Krikorian et al., 2012; Smith et al., 2010a; Witte et al., 2009). These are surprisingly short interventions to show significant effects. One of these studies was among older adults with MCI (Krikorian et al., 2012) and showed significant effects on memory after just 6 weeks. This is a high risk group for the development of dementia. The potential for targeted intervention using weight loss to promote neurocognitive health among this high risk group should not be overlooked.

In conclusion, while the results of dietary weight loss interventions show mixed effects on cognitive function there is evidence to suggest that they can have cognitive benefits, perhaps particularly for memory. Relative to observational studies, these interventions were of short duration (max 12 months) and had short follow-up periods. Further research is needed to determine the long-term effects of calorie restricted weight loss diets on human cognitive function.
3.4 Dietary Composition and Frequency

3.4.1 Quality of Diet

Dietary composition could also have differential effects on obesity-related factors such as insulin sensitivity, dyslipidemia, or BDNF, with consequent effects on neurocognitive health. Consistent with this, different weight loss diets can have different effects on cognition and some effects can be independent of weight. The effects of various dietary components on cognitive decline and dementia risk have been extensively reviewed elsewhere (Plassman et al., 2010), and a full review of this large body of literature is beyond the scope of this dissertation. However a few examples can highlight some of the results that have been found for differences in macronutrient content. In a study comparing isocaloric low carbohydrate or standard dietary restriction diets, D’Anci, Watts, Kanarek, and Taylor (2009) found that dieters on the standard caloric restricted diet performed better on memory-based tasks, but worse on measures of vigilance and attention. In another study, a comparison of two 30% calorie restricted diets in overweight and obese women (BMI 26-43, mean age 50.2 years) found that although a low carbohydrate ketogenic diet produced less weight loss than an isocaloric high carbohydrate low fat diet (6.6 vs. 8.0% body weight) both diets improved speed of processing and working memory (Halyburton et al., 2007). Since effects remained significant after controlling for weight lost, factors other than absolute weight loss may have been in play.

3.4.2 Ketogenic Diets

The ketogenic provides a distinctive example of the effects of macronutrient differences on neurocognitive health. The ketogenic diet (KD) is a low carbohydrate, high-fat diet intended to induce and sustain a state of ketosis in the body by minimizing somatic glucose (Hallbook, Ji, Maudsley, & Martin, 2012; Zupec-Kania & Spellman, 2008). Though it can be highly restrictive (Miranda, Turner, & Magrath, 2012) and may lead to some reductions in caloric intake
(Cullingford, 2004), the KD is not considered a form of caloric restriction. The person on a KD usually consumes the majority of their calories from fat, as well as 1g of protein per kilogram of body weight and around 5-10g of carbohydrates daily (Kossoff, 2004). This increases circulating free-fatty acids and promotes fatty acid oxidation, leading to a state of ketosis (Henderson, 2008).

While the anti-convulsant properties of KD are well-recognized, and their use in treating seizures widespread, evidence now also suggests that the KD is neuroprotective and that the mechanisms are similar to those of caloric restriction. (Maalouf, Rho, & Mattson, 2009). Effects on cognitive function, including memory performance, have also been reported. For example, in patients with AD, the KD has been found to enhance cognitive activity (Reger et al., 2004, in Maalouf et al, 2009). Consistent with this, KDs have been found to reduce beta-amyloid burden in mice (Van dA et al., 2005). Cognitive benefits can be observed even if the KD is begun in older age, as has been demonstrated in rats (Xu et al., 2010).

The KD may have neuroprotective effects for diseases in which oxidative damage is implicated. KD may improve mitochondrial function while also lowering production of reactive oxygen species (Hallbook et al., 2012; Maalouf et al., 2009). The change in macronutrient content may also alter insulin signaling, with beneficial effects consistent with the insulin hypothesis previously described ((Craft & Stennis Watson, 2004; Henderson, 2008). These potential improvements in metabolic efficiency, insulin signalling could make it an attractive way to treat AD and other neurological diseases of aging where oxidative stress is implicated (Henderson, 2008).

Despite the mounting evidence for anticonvulsant and neuroprotective effects of the ketogenic diet, can also have adverse effects that make widespread use in the population unlikely. These can include hunger, gastrointestinal effects, nephrolithiasis, hyperlipidemia and
slowed growth (Hartman & Vining, 2007; Kang, Chung, Kim, & Kim, 2004; Kwiterovich, Vining, Pyzik, Skolasky, & Freeman, 2003; Mosek, Natour, Neufeld, Shiff, & Vaisman, 2009). Deficits in learning and memory, and impaired brain growth have also been reported (Zhao, Stafstrom, Fu, Hu, & Holmes, 2004). It is possible this was due to malnutrition rather than the macronutrient content (Cunnane & Likhodii, 2004). In addition to these potential adverse effects the ketogenic diet may be considered less palatable than a diet containing more carbohydrates. For these reasons a more safe and acceptable alternative is being sought.

Since ketone bodies might mediate the neuroprotective effects of KDs, fasting and intermittent fasting may provide viable alternatives.

3.4.3 Fasting

Fasting is commonly used for weight reduction purposes or for religious reasons; however its effect on cognitive function in humans has been poorly studied. Over time, fasting reduces the amount of glucose readily available as an energy source in the brain (Owen et al., 1967). Under complete starvation the brain will eventually obtain its energy from ketone bodies, which have been shown to have neuroprotective effects (Maalouf et al., 2009). Fasting has other effects on the body which might affect cognition indirectly. These include reduced insulin sensitivity (Duska, Andel, Kubena, & Macdonald, 2005; Johnston et al., 2006; Newman & Brodows, 1983), changes in lipid profiles (Bayer et al, 1997), and reduction of serum leptin levels (Ahima et al., 1996).

Though little research into the cognitive effects of fasting has been conducted, some studies of brief fasting show mild reductions in cognitive function. For example Pollitt and colleagues (Pollitt, Cueto, & Jacoby, 1998) demonstrated a reduction in stimulus discrimination, an increased in errors, and slower memory recall in children fasting overnight and during the morning compared with children who fasted overnight only. They also showed that missing
breakfast correlated with adverse effects on children's late morning problem-solving performance (Pollitt, Lewis, Garza, & Shulman, 1982). Doniger and colleagues (Doniger, Simon, & Zivotofsky, 2006) showed that fasting was associated with cross-domain deficits for tasks requiring perception of spatial relations in subjects completing a 12 to 16 hour fast. Other authors showed fasting caused heterogeneous and domain specific changes (Lotfi, Madani, Tazi, Boumahmaza, & Talbi, 2010; Tian et al., 2011). By contrast others found no detrimental effects in 10 days of fasting in the obese (Liebermeister & Schrotter, 1983).

3.5 Intermittent Fasting

While it is often assumed that the beneficial effects of calorie restriction (CR) are due to weight loss, or the fact that calorie restricted animals weigh proportionally less than their ad libitum fed counterparts, this is not necessarily the case. Not only do human studies indicate that different diets have different effects on cognition, but animal studies demonstrate that altering the frequency of food intake may produce similar or greater neurocognitive effects than CR.

Intermittent fasting (IF) is a form of dietary restriction in which organisms alternate between periods of complete fasting and ad libitum feeding. The most commonly researched form of IF involves alternating fed and fasted days, or alternate day fasting. Like CR, IF produces significant improvements in lifespan and animal health (Goodrick, Ingram, Reynolds, Freeman, & Cider, 2009) (Anson et al., 2003a; Azab, Khabour, Al-Omari, Alzubi, & Alzoubi, 2009; Lee et al., 2006b; Sogawa & Kubo, 2000; Sohal & Weindruch, 1996), and many of the effects of IF are similar to those of prolonged CR (Mattson, 2005).

However the effects of IF may be independent of weight loss, as was demonstrated in an elegant study by Anson and colleagues (Anson et al., 2003b), in which rodents on an IF diet showed greater health benefits than pair fed CR controls. Furthermore, the beneficial effects of
IF may be greater than those found in CR. For example Duan et al. (2001a) demonstrated that a 15% caloric deficit with IF produces greater resistance to excitotoxic damage to hippocampal neurons, and larger increases in other markers of neurocognitive health than 30% CR.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CR</th>
<th>IF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning &amp; memory</td>
<td>Improved</td>
<td>Improved (animal models)</td>
</tr>
<tr>
<td>BDNF</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>Synaptic plasticity</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>Neurogenesis</td>
<td>No change</td>
<td>Increase</td>
</tr>
<tr>
<td>HSP70</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>Body weight</td>
<td>Decrease</td>
<td>Decrease or no change</td>
</tr>
<tr>
<td>Body fat</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Body temperature</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Blood insulin</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>IGF-1 levels</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>IL-6</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>β-Hydroxybutyrate</td>
<td>Unchanged</td>
<td>Increase</td>
</tr>
<tr>
<td>HDL</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>Decrease</td>
<td>Decrease</td>
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</table>

*Adapted from Mattson, Duan and Guo, 2003.*

**Animal Studies of Intermittent Fasting**

In animal models IF does appear to produce additional health benefits beyond those seen after CR. As can be seen in Table 3.5.1, both diets decrease fasting glucose and insulin, as well as heart rate and blood pressure in animal models (Anson et al., 2003b; Wan, Camandola, &
However, the magnitude of improvement in insulin sensitivity can be greater in IF (Anson et al., 2003b). Intermittent fasting also differs from CR by increasing circulating insulin-like growth factor (IGF)-1, which is decreased in animals on a CR diet (Anson et al., 2003b). Interestingly, IGF-1 may play a role in β-amyloid clearance from the brain, with significant implications for the development of the hallmark β-amyloid plaques seen in Alzheimer’s disease (Carro et al., 2002; Craft, 2007). Another difference between IF and CR are their effects on the neuroprotective Brain-Derived Neurotrophic Factor (BDNF), with larger increases after IF than are seen in CR (Duan et al., 2001b).

Animal studies show that IF improves learning and memory in ways similar to CR, but with additional neurocognitive benefits (Mattson et al., 2003). As with CR, improvements in learning and memory are seen – with corresponding improvements in neural health, including increased synaptic plasticity and increased neural resistance to excitotoxic insult and age-related neurodegeneration (Bruce-Keller et al., 1999; Duan et al., 2001a; Yu & Chung, 2001). Yet unlike CR, IF also increases neurogenesis in the brains of adult rats and mice, particularly in the hippocampus, an area well known for its role in learning and memory, and among the first brain regions affected in AD pathology (Duan et al., 2001b; Gage, 2000; Lee et al., 2000; Lee, Duan, & Mattson, 2002). It is perhaps relevant that neurogenesis is typically impaired in mice that have low BDNF (Lee et al., 2002).

**Human Studies of Intermittent Fasting**

The effects of IF on human cognition have not yet been tested, but several human experiments with IF to date suggest that general health benefits parallel those seen in animal models. Normal weight men and women aged 20-55 years on an IF regimen for 3 weeks decreased their body weight by approximately 2kg and insulin sensitivity improved for
men, though not women (Heilbronn, Smith, Martin, Anton, & Ravussin, 2005), and showed no change in fasting glucose, but did show decreases in fasting insulin. Likewise Halberg et al. (2005) found that normal weight men on an IF diet for 2 weeks who were instructed to fully compensate for their fasting day lost no weight but still showed improved insulin-mediated glucose uptake. Johnson et al (2008) placed obese adults with asthma on a modified IF regimen, in which they ate <20% of normal daily intake on their restricted day, and *ad libitum* the next. Nine of the ten participants adhered to the diet and lost an average of 8% of their body weight over the 8 week period. In this sample IF diet improved asthma-related symptoms, and decreased inflammation (serum TNF-α), but decreased BDNF. While animal studies show increased BDNF after IF, they also show that BDNF can be elevated in response to potential neuronal threats such as inflammation. It is possible that these asthma patients started with high BDNF as part of their asthma, which was normalized alongside the asthma and inflammation after the intervention. In all other respects results in humans are consistent with those seen in animal models of IF. It is therefore possible that neurological and cognitive effects of IF would also be comparable. Since beneficial effects of IF on health appear to be independent of weight loss, research into the effects of IF on human cognition could potentially provide a means of improving cognitive health of obese adults, even if weight loss is not achieved. IF may also provide some valuable insights into potential mechanisms linking obesity and cognitive function.

**Adverse Effects of Intermittent Fasting**

Human and animal studies of IF have widely report reported beneficial effects of IF on health. The brief duration of fasting typically used (~1 day) may contribute to a lower likelihood of the adverse effects than can be found in prolonged fasting. However it remains possible that
IF could have adverse effects, particularly on perceived hunger, mood, hydration and nutritional adequacy. Among studies of IF in humans to date, one minor unfavorable change was reported by Heilbronn et al, (Heilbronn et al., 2005) who found an unfavorable rise in glucose among women but not men after 3 weeks of IF.

Natural instances of variants of IF may also provide some insight into its potential effects on health. Ramadan fasting may be one such example. Ramadan is a month of the Muslim calendar during which Muslims abstain from eating or drinking between sunrise and sunset. It is therefore a form of intermittent, though not alternate day, fasting. During Ramadan subjective alertness and mood have been shown to decrease (Roky, Iraki, HajKhlifa, Lakhdar Ghazal, & Hakkou, 2000), as well as psychomotor performance (Roky, Houti, Moussamih, Qotbi, & Aadil, 2004), and an increase in daytime sleepiness has been reported (Roky et al., 2003).

However Ramadan fasting typically produces significant changes to sleeping patterns and duration, for all food must be consumed after sunset and before sunrise, and many practitioners will stay up late to fit in their normal daily caloric intake during these hours (Roky et al., 2000). In addition, drinking during daylight hours is also restricted, so practitioners may experience dehydration. Hence the detrimental effects of Ramadan that have been reported may be due to sleep deprivation and/or dehydration (Suhr, Patterson, Austin, & Heffner, 2010).

**Mechanisms of Intermittent Fasting**

While the distinctive mechanisms of IF are not fully understood, some researchers theorize that IF-specific effects are due to activation of the physiological repair mechanisms that are part of a normal response to stress (Martin, Mattson, & Maudsley, 2006; Mattson & Calabrese, 2010; Mattson et al., 2003). Fasting is psychologically and physiologically stressful (Mamczar, 2000; Mattson et al, 2000). Physiologically, reduced availability of glucose is a threat to neuronal integrity (Buckner, Snyder, Sanders, Raichle, & Morris, 2000; Vaishnavi et al., 2010),
so energy deficits lead to counter-regulatory mechanisms to ameliorate the threat of hypoglycemia. Short-term fasting therefore leads to an increase in the aptly named glucocorticoid (GC) stress hormones - cortisol in humans, corticosterone in rodents – which mobilize glucose from storage (Hanniman, Lambert, Inoue, Gonzalez, & Sinal, 2006; Lee et al., 2006a) once a single episode of fasting is a stressful, IF therefore involves repeated exposure to a mild metabolic stressor (glucose deprivation), a stress response (GC secretion), and the opportunity for recovery in-between exposures. Consistent with this theory, animal models indicate that the repeated exposure to short-term fasting that occurs in IF produces metabolically stressful energy deprivation and increases GC production (Mager et al., 2006; Varady & Hellerstein, 2007; Yu & Chung, 2001). Furthermore, rodents treated with a competitive inhibitor of glycolysis (2-deoxy-D-glucose) show physiological effects similar to those of IF (Mamczar, 2005). These findings suggest that IF does in fact produce repeated mild metabolic stress in animals.

**Hormesis** is a term used by toxicologists to refer broadly to any biphasic dose-response in which a low dose produces beneficial effects while a high dose produces harmful effects (Calabrese et al., 2007; Mattson, 2008). A wide variety of stressors can have hormetic effects, including exposure to heavy metals, pesticides, antibiotics, chemotherapeutic agents, ethanol, chloroform, hypergravity, cold, ionizing radiation and energy deficit by fasting or physical activity (Calabrese, 2008a; Calabrese & Cook, 2006). The same stress-dose response is seen in many psychological functions, and is referred to as the Yerkes-Dodson law in psychology (Calabrese, 2008b). Thus exposure to many different stressors leads to the fundamental biphasic inverse U shaped curve (Calabrese & Baldwin, 2001, 2003; Depke et al., 2008), shown in Figure 3.5.1, that is so familiar in stress research (Mattson & Cheng, 2006; Rattan, 2008).
Figure 3.5.1. An inverse U-shaped dose response curve.

While a large body of literature demonstrates that severe stress can have detrimental effects on health (Chrousos & Gold, 1998), a growing body of evidence suggests that repeated exposure to mild stressors could have beneficial effects. While this remains controversial and under ongoing investigation, beneficial effects have been reported for a wide variety of different physiological stressors, including physical activity, heat shock, irradiation, pro-oxidants, hypergravity and curcumin, can have general health benefits similar to those found with IF fasting (Calabrese & Baldwin, 2001). These effects include anti-aging and life-prolonging effects (Calabrese & Cook, 2006; Rattan, 2008), preservation of pancreatic β-cells (Bates, 2008), improved immune regulation (Bauer, 2001), and enhanced metabolic efficiency (Roth, Ingram, & Lane, 1999; Sohal & Weindruch, 1996; Weindruch & Walford, 1988). Organisms exposed to small doses of these stressors appear to adapt, compensate, and show protection against future exposures (Calabrese & Baldwin, 2001). Interestingly, mild exposure to one stressor may confer resilience against other different (heterotypic) stressors, suggesting a common mechanism (Masoro, 2000). It has therefore been proposed that repeated exposure to mild stressors can
progressively condition an organism towards resilience against stress (Masoro, 2000; Mattson & Calabrese, 2010).

Figure 3.5.2. Repeated episodes of stress in the mild-moderate “beneficial” range may have cumulative beneficial effects.

Intermittent fasting may increase resilience to stress by triggering protective repair mechanisms normally activated in response to stress (Bruce-Keller et al., 1999; Duan, Guo, Jiang, Ware, & Mattson, 2003b; Duan & Mattson, 1999; Martin et al., 2006; Maswood et al., 2004). Insulin-like growth factor (IGF)-1 may be one example. This protective growth mechanism is upregulated after IF and after physical activity, but not after CR (Anson et al., 2003b; Duan et al., 2001b; Mattson et al., 2003). The increased BDNF found after IF may be another example. This neurotrophin shows neuroprotective effects, and is involved in neurogenesis, synaptic plasticity, and neurotransmitter synthesis (Diogenes et al., 2007; Mattson et al., 2003). Neural BDNF production increases in response to cellular stressors that could cause neuronal damage, such as hypoglycemia, trauma, ischemia, or seizures, and can protect neurons against death (Mattson et al., 2003). BDNF also appears to protect neurons in experimental models of AD and Parkinson’s
disease (Duan et al., 2001a). Upregulation of BDNF after IF may therefore be one case in which mild stress leads to beneficial increases in repair.

The release of GC stress hormones such as cortisol may also be part of the stress response to IF. As mentioned above, low doses of cortisol can have beneficial effects on the brain and cognitive function (Lupien et al., 2005b; McEwen, 2000). These hormones are released by the Hypothalamic Pituitary Adrenal (HPA) axis, a primary stress response system, which may be required as part of the adaptive response to IF. This is suggested by the effects of IF on a transgenic mouse model of AD – the APP mutant mouse. The APP mutant mouse model of AD shows not only increased amyloid deposition in the brain but also has abnormal glucose regulation and GC responses to restraint stress (Pedersen, Culmsee, Ziegler, Herman, & Mattson, 1999). When placed on an IF dietary regimen they are apparently unable to mount a counter-regulatory response to the fasting, instead becoming severely hypoglycemic on their fasted days and dying within 2-3 weeks (Pedersen et al., 1999). This is consistent with the view that the stress response plays an important role in the effect of IF (Martin et al., 2006).

In other rodent strains IF appears to improve general stress resistance (Mager et al., 2006; Varady & Hellerstein, 2007; Yu & Chung, 2001). Intermittent fasting has also been shown to downregulate glucocorticoid receptors, while maintaining mineralocorticoid receptors (Lee et al., 2000). However the effects on general HPA axis diurnal rhythm are unknown, as the sample collection methods required in animal models are stressful, making it difficult to obtain repeated measures across the day. Thus it may be that the stress response is an important part of the beneficial adaptation to IF, though this needs further testing.

The effect of IF on human stress response and HPA axis function has not yet been adequately tested. The only human study to measure cortisol during a modified intermittent fasting paradigm collected samples just once a day and did not control time of day for sample
collection (Stote et al., 2007). Since cortisol follows a strong diurnal rhythm this may have confounded the results. The evidence from animal studies suggests that it is worth investigating not only whether IF can benefit human learning and memory, but also the relationship of any such alterations to changes in resilience to stress. This is particularly important because of the body of literature demonstrating that stress can have significant detrimental effects on human cognition.
4. Study 4: the DRIFT Study

4.1 Introduction

Given recent epidemiological evidence linking obesity to cognitive decline and dementia described above, interventions that have the potential to reduce obesity and improve cognitive function could be valuable. Animal studies show significant neuroprotective effects for IF, including protection against age-related declines in learning and memory, improved synaptic plasticity and neural health, increased neurogenesis, increased brain-derived neurotrophic factor, resilience against neurotoxic insult, and increased resistance to neurodegenerative diseases (Martin et al., 2007a; Mattson et al., 2003; Mattson & Wan, 2005). (Anson et al., 2003b; Martin et al., 2006). Intermittent fasting is a dietary restriction regimen in which organisms alternate between periods of complete fasting and periods of ad libitum feeding. However the effects of IF on human cognition have not yet been tested. While many of the effects of IF are similar to those found in calorie restricted (CR) diets, Animal studies also show other significant health benefits for IF, including improved insulin sensitivity (Mattson & Wan, 2005). This effect has been replicated in studies of IF in healthy weight (Halberg et al., 2005) and obese humans (Johnson et al., 2007). It is possible that the neurocognitive benefits seen in animals are also replicable in humans, but this remains to be tested.

If IF affects human neurocognitive health it will also be important to understand its mechanisms of action. Results from animal and human studies show that IF can affect some of the mechanisms that could link obesity to AD, including glucose regulation and insulin resistance, IGF-1, leptin, BDNF, inflammation, and glucocorticoids (Martin et al., 2006; Mattson, 2005; Mattson & Calabrese, 2010; Mattson et al., 2003; Mattson & Wan, 2005). Interventions that enhance these factors in midlife, when the underlying “pre-clinical” pathology of AD appears to begin (Heilbronn et al., 2005; Johnson et al., 2007; Sperling et al., 2011), may be particularly
useful in preventing cognitive decline. While weight loss by calorie restricted diets can be a useful way to study these mechanisms, evidence indicates that IF can have unique effects - suggesting that some different mechanisms are involved. For example IF has been shown to increase neurogenesis and IGF-1 in animals, while CR does not (Mattson, 2005; Mattson et al., 2003). In addition evidence suggests that glucose regulation and BDNF are better in IF fed animals relative to pair-fed calorie restricted controls (Anson et al., 2003b). In humans, beneficial effects of IF on glucose regulation were apparent in healthy young men who were instructed to maintain a stable weight (Halberg et al., 2005), suggesting that some effects on health could be independent of weight loss.

Intermittent fasting could therefore have neuroprotective effects and may provide a useful opportunity to study the mechanisms linking obesity and cognitive function in midlife. To test this we conducted a randomized controlled trial to investigate 1) the safety and efficacy of IF for weight loss among obese adults, 2) the effects of IF on cognitive function among obese adults, 3) explore the potential mechanisms by which IF might affect neurocognitive health outcomes. We hypothesized that IF would have similar effects to those previously described in animals, including cognitive improvements specific to learning and memory, increased BDNF, improved insulin sensitivity, reduced inflammation and increased resilience against stress, and explored the possibility that effects on memory function may be mediated by these

4.2 Methods

4.2.1 Participants

Twenty-six obese (BMI 30-45 kg/m²) but otherwise healthy community volunteers, recruited through community flyers and advertisements, took part in the study. Participants were eligible to be included if they were obese but otherwise healthy, had no evidence of depression (CESD, Radloff (1977), showed no evidence of binge-eating disorder (Questionnaire
of Eating and Weight Patterns: Spitzer, Yanovski, and Marcus (1993), English was their first language and they were able to read and write to a 6th grade level. Participants were recruited using IRB-approved advertisements placed around the campus of the University of Colorado Denver and IRB approved email advertisements through the University list-serv. Full informed consent was sought and documented before study participation. This study was reviewed and approved by the Colorado Institutional Review Board COMIRB Protocol 06-0383.

Participants were paid up to $800 for taking part in the study. This included $50 for the test fast, $75 for each of the baseline study visits, $350 for completion of the one-week in-patient study at the beginning of the weight loss period, $150 for completion of visits at 8 weeks, and $100 for the 6 month follow-up visit.

**Sample Size and Power Calculations**

Sample size for the DRIFT study was chosen to provide the power to detect statistically significant changes in weight between the intervention and control groups. The minimum clinically meaningful difference in weight was determined to be 1 kg. Sample size to detect this difference was calculated using 1) pilot data from the PI (WTD) of an 8 week CR protocol (weight loss of 6.0 ± 2.8 kg) and pilot data from an 8 week IF protocol with n=2, (weight loss of 11.25 ± 3.3 kg) as well as 2) extrapolations from other studies of general fasting (Jackson et al., 1971; Runcie & Thomson, 1970) Johnstone et al, 2002; Oh, Kim and Choe, 2002) and allowing for ~20% compensation (per day) on a feast day (Johnstone et al, 2002). To detect an anticipated 15kg weight loss in the IF group, with 30% variance (15 ± 4.5 kg) a sample size of 7 per group was required to 90% power with an α of 0.025. In order to account for potential dropout 15 per group were recruited. It was determined unlikely to detect statistically significant differences in
insulin sensitivity, cortisol or other physiological markers so these were considered exploratory aims.

4.2.2 Intervention Protocols

The DRIFT study used an experimental randomized controlled design. A flow diagram of the study design can be seen in Figure 4.2.1. In brief, after baseline assessment of metabolic, behavioral and cognitive function after both a fed day and after a short-term fast, participants were randomized to either 8 weeks of a standard calorie restricted diet (SDR), or to 8 weeks of intermittent (alternate day) fasting (IF). During the study, all participants were admitted to the Clinical Translational Research Center (CTRC) at the University of Colorado Hospital on 6 separate occasions for monitoring. These visits included: 1) a test fast to test the safety and tolerability of fasting for each potential participant, 2) baseline fed visit, 3) baseline fasting visit, 4) week 1 visit, 5) week 8 visit, 6) 6 month follow-up. A more detailed description of the procedures used on these visits is given below.
4.2.3 Materials and Tests

Assessment of Cognitive Function

Cognitive function was assessed by performance on a computerized test battery administered at 7am each day of in-patient visits. The CNS Vital Signs test battery (Psychology Software Tools, Inc. Pittsburgh, PA) was administered on a laptop PC and administered in a quiet private hospital room free of distractions or interruptions. The CNS Vital Signs test was developed for repeated measures testing purposes and aims to minimize practice effects. Test-retest reliability is 0.67 – 0.85 (CNS Vital Signs). Each test administration takes approximately 20

<table>
<thead>
<tr>
<th>Test Fast</th>
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<tbody>
<tr>
<td>Baseline Fed (n=26)</td>
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<tr>
<td>4 weeks passes</td>
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<tr>
<td>Baseline Fast (n=26)</td>
</tr>
<tr>
<td>n=12 randomization n=14</td>
</tr>
<tr>
<td>SDR Week 1 Fed Fed</td>
</tr>
<tr>
<td>IF Week 1 Fed Fasted</td>
</tr>
<tr>
<td>SDR Week 8 Fed Fed</td>
</tr>
<tr>
<td>IF Week 1 Fed Fasted</td>
</tr>
<tr>
<td>6 month follow-up</td>
</tr>
</tbody>
</table>

Figure 4.2.1. Overview of the DRIFT study design.
minutes. Participants responded on the standard computer keyboard using pre-specified keys.

The CNS Vital Signs test battery is comprised of 7 subtests, administered in a fixed order.

Verbal Memory Test (VBM): This test is an adaptation of the Rey Auditory Verbal Learning Test (Taylor, 1959; Rey 1964). Respondents are required to remember 15 words and recognize them in a field of 15 distracters. The test is repeated at the end of the test battery. Low scores indicate verbal memory impairment.

Visual Memory (VIM): This test is based on the Rey Visual Design learning test. Respondents are asked to remember 15 geometric figures and recognize them in a field of 15 distracters. The test is repeated at the end of the battery. Low scores indicate memory impairment.

Finger-tapping test (FTT): Developed by Mitrushina et al, (1999), this task measures motor speed and fine motor control. Respondents tap a key as quickly as they can in 3 rounds. Low scores indicate motor slowing.

Symbol Digit Coding (SDC): Symbol digit coding is a 2 minute test that measure of psychomotor speed and visuo-motor coordination. The test is very sensitive to aging, and errors may be due to impulsive responding, misperception or confusion.

Stroop Test (ST): The Stroop task (Stroop, 1935) is comprised of three types of trials: a) color words (red, green, yellow), b) neutral words to match the color words in length and frequency of occurrence: intent, lot, ship, advice, cross, debate (Battig & Montague, 1969), and c) a string of asterisks with lengths varying to match the lengths of the color words. The stimuli were presented in one of three colors (red, green or yellow) centered on a black background. It measures processing speed, cognitive flexibility and cognitive inhibition. Prolonged reaction times may indicate cognitive slowing, while errors may indicate impulsiveness or disinhibition.
Shifting Attention Test (SAT): In this test of executive function respondents need to adjust their responses to randomly changing rules. The best scores have many correct responses, few errors and a short reaction time. Continuous Performance Test (CPT): The CPT is a measure of vigilance or sustained attention or attention over time (Rosvold et al, 1956). It is sensitive to CNS dysfunction in general, and is not specific to any particular condition (Riccio & Reynolds, 2001).

The scores of these tests were used to automatically generate cognitive domain scores, as outlined in Table 4.2.1. These domains were memory, attention, cognitive flexibility, cognitive speed and reaction time.

<table>
<thead>
<tr>
<th>Table 4.2.1. CNS vital signs cognitive test domains and how they are calculated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
</tr>
<tr>
<td>Attention^</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
</tr>
<tr>
<td>Psychomotor speed</td>
</tr>
<tr>
<td>Reaction time^</td>
</tr>
</tbody>
</table>

^ Lower scores indicate better performance.

Assessment of Stress

Both psychological and physiological measures of stress were assessed.

Psychological stress: To assess psychological stress, participants were asked to rate their perceived stress and their mood in two questionnaires, which were administered at approximately 7am of each study visit, directly before the cognitive test battery.

The 10-item Perceived Stress Scale (PSS: Cohen, Kamarck, and Mermelstein (1983)) is a self-report questionnaire in which respondents rate on a 5 point Likert-type scale ranging from...
“never” to “very often” how often they have experienced symptoms of perceived stress. For example “In the last week, how often have you felt that you were unable to control the important things in your life?” The PSS was added late to the study and was administered to a subsample of participants.

The Profile of Mood States (POMS) is a self-report inventory in which participants rate how well a list of mood states (such as “friendly”, “tense” or “confused”) matches how they have been feeling. The DRIFT study used the “immediate” and “over the last week” versions of the 30-item POMS Brief form. Items correspond to 6 identifiable mood states including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Participants respond on a 5-point Likert-type scale ranging from “not at all” to “extremely”. Scoring followed test instructions on reverse coding and summation of items to create a) a total mood score, and b) a subscale for tension/anxiety.

**Physiological stress:** Physiological measures of stress were based on two different measures of cortisol.

*Basal diurnal cortisol.* During in-patient visits, participants gave saliva samples at 6:00am, 6:30am, 7:00am, and every 2 hours thereafter while they were awake. These samples were analyzed by standard laboratory assays (Salimetrics) to assess basal cortisol. Basal cortisol was used to calculate peak morning cortisol (standardized as half an hour after waking, i.e. at 6:30am of each study visit), evening nadir (standardized as cortisol at 21:30pm on each study visit). To assess cortisol rhythm, these values were used to calculate daily cortisol decline, which was calculated as the difference between the morning peak and the evening nadir. Cortisol decline was not available for the 6 month follow-up, as participants did not spend 24h at the in-patient visit.
**Stimulated stress response.** At each visit participants completed a 90% VO₂ max exercise stress test, which acted as a stimulated HPA axis stressor. This exercise stress test avoids issues of “training” bias, a factor seen frequently with other physiologic hypothalamic level stressors (e.g., mental stress tests) because the same relative exercise intensity results in similar magnitude of change in HPA axis activity across different fitness levels. Hence responses can be compared between participants with widely different absolute maximal aerobic capacities. In the 90% VO₂ max stress test participants walked on a treadmill for 5 minutes to warm up. This was followed by an increasing grade and speed until they were working at 90% of VO₂ max (maximum assessed at baseline) for 10 minutes. Blood was drawn and saliva samples collected for measurement of salivary cortisol at 0, +15, +25, +35, +45, +55, +65 and +75 minutes while the participant was seated and resting quietly. Cortisol values were used to calculate area under the curve (AUC) as an estimate of cortisol response to the exercise stress test.

**Assessment of Depressive Symptoms**

Symptoms of depression were assessed at baseline and post-intervention using the Center for Epidemiological Studies Depression scale (CESD: (Radloff, 1977)). The CESD is a 20 item self-report scale intended to measure depressive symptoms in the general population. Participants answer on a 4 point Likert-type scale how often they feel depressive symptoms such as tearful, lonely, sad or inadequate. Reliability in the general population has been assessed (r=0.85, patient samples 0.90, (Radloff, 1977)). Scores were summed according to CESD scoring instructions. Total CESD score was recorded for baseline and post-intervention.

**Assessment of Disordered Eating Behaviors**

The Questionnaire of Eating and Weight Patterns (QEWP: (Spitzer et al., 1993)) is a screening test for eating disorders and was administered at baseline to screen out potential participants with eating disorders, such as binge-eating disorder. It was also administered after
the 8 week intervention to determine whether the IF intervention increased disordered eating patterns. Eating disorder status was coded as a dichotomous variable (yes/no).

**Assessment of Adiposity**

Participants’ height and weight (kg) were measured by standard methods. Percentage of body fat and percent trunk fat were determined using a Dual X-ray Anthropometry (DXA) scan at baseline, week 8 and at 6-month follow-up.

**Assessment of Insulin Sensitivity (SI)**

Insulin sensitivity was assessed on the final day of each study visit using a Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT). In this test, two intravenous lines were placed into ante-cubital veins in each arm. A 20% glucose solution was infused gradually over the span of 15 minutes into one arm. Blood was drawn from the other arm for analysis of glucose and insulin at regular intervals, giving 30 time points over 180 minutes after the full glucose load was delivered. Insulin sensitivity was calculated using MinMod Millenium (Pacini & Bergman, 1986), a computer package which can be used to estimate insulin sensitivity from the dynamics of glucose-insulin collected by FSIVGTT. Insulin sensitivity was measured on the final day of each study visit.

**Laboratory Measures**

Blood collected from participants during in-patient hospital visits was analyzed for electrolytes, glucose, insulin, free fatty acids, leptin, ghrelin, ketones (3-OH-butyrate and acetoacetate), and triglycerides using standard laboratory procedures in the CTRC core laboratory. A 24-hour urine collection was also collected for analysis of nitrogen, cortisol, epinephrine, and norepinephrine. Markers of inflammation, including serum interleukin-6 (IL-6), C-reactive protein (CRP), and plasma Tumor Necrosis Factor-α (TNF-α) were also assayed using Enzyme-Linked ImmunoSorbent Assay (ELISA, R&D systems). For analysis of BDNF, plasma
samples were sent to collaborators Mark P. Mattson and Bronwen Martin at the National Institutes on Aging because of their experience with this difficult assay. As a result BDNF was assessed using the blood drawn at 7am of each study visit.

4.2.4 Procedure

Screening

Inclusion and exclusion criteria were assessed at a) phone screening, and b) in-person screening by a professional research assistant and a physician. In-person screening involved a comprehensive medical examination to ensure participants met selection criteria and that they were in good health. This visit included a medical examination, laboratory measures, the QEWQ, CESD and anthropometric measures. Participants were excluded if they reported >10lb weight change in the last 6 months, had presence or history of a chronic disease known to affect appetite, food intake or metabolism, including hypothyroidism and cancer, used medications known to affect appetite, were pregnant or currently lactating, were a current smoker, had a history of cardiovascular disease, renal disease, hepatic disease, seizures, migraine, or disorder of the gastrointestinal tract.

Test Fast

The test fast was conducted in order to determine safety and tolerability of fasting for each participant. Participants reported to the CTRC at the University of Colorado Hospital at 7pm and were admitted as in-patients. They ate no food for the remainder of the evening, and were asked to go to bed at 10pm. Participants were woken at 6:30am and gave a saliva sample, collected in a small tube. This was followed by measurement of resting metabolic rate (RMR), another saliva sample, echocardiogram (ECG), saliva sample, and the VAS & POMS questionnaires. After another saliva sample, blood was drawn at 7am (for glucose, insulin, electrolytes, triglycerides, free fatty acids, ketones, complete blood count, ghrelin, and leptin),
followed by the cognitive computer battery. Participants fasted for the rest of the day but were allowed free access to water and non-caloric beverages, including caffeinated beverages. They remained in the hospital for monitoring for the rest of the day and slept overnight again at the CTRC. The same series of tests were conducted before the participant was given breakfast and discharged home. After the test fast, only participants who reported that they tolerated the fast well and who did not have adverse changes in safety data were continued in the study.

Baseline Visits

<table>
<thead>
<tr>
<th>BASELINE VISIT PROCEDURE</th>
</tr>
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<tbody>
<tr>
<td><strong>FED VISIT</strong></td>
</tr>
<tr>
<td>Subject admitted to in-patient CTRC 1900pm day 0</td>
</tr>
<tr>
<td><strong>DAY 1</strong></td>
</tr>
<tr>
<td>600am; Saliva, RMR.</td>
</tr>
<tr>
<td>630am: Saliva.</td>
</tr>
<tr>
<td>Cognitive test,</td>
</tr>
<tr>
<td>Questionnaires.</td>
</tr>
<tr>
<td>Saliva at: 900, 1100, 1300, 1500, 1300, 1500, 1700, 1900, 2000, 2100, 2130, 2200.</td>
</tr>
<tr>
<td><strong>Subjects eat meals</strong></td>
</tr>
<tr>
<td><strong>DAY 2</strong></td>
</tr>
<tr>
<td>600am; Saliva, RMR.</td>
</tr>
<tr>
<td>630am: Saliva.</td>
</tr>
<tr>
<td>Cognitive test,</td>
</tr>
<tr>
<td>Questionnaires.</td>
</tr>
<tr>
<td>Insulin Sensitivity (FSIVGTT)</td>
</tr>
<tr>
<td>90% VO2max</td>
</tr>
<tr>
<td>Discharged</td>
</tr>
</tbody>
</table>

| **FASTED VISIT**          |
| Subject admitted to in-patient CTRC 1900pm day 0 |
| **DAY 1**                 |
| 600am; Saliva, RMR.       |
| 630am: Saliva.            |
| Cognitive test,           |
| Questionnaires.           |
| Saliva at: 900, 1100, 1300, 1500, 1300, 1500, 1700, 1900, 2000, 2100, 2130, 2200. |
| **Subjects DO NOT EAT.**  |
| **DAY 2**                 |
| 600am; Saliva, RMR.       |
| 630am: Saliva.            |
| Cognitive test,           |
| Questionnaires.           |
| Insulin Sensitivity (IVGTT) |
| 90% VO2max               |
| Discharged                |

Figure 4.2.2. Baseline fed and baseline fasted visits compared.

Participants attended two separate baseline visits – one fed and one fasted. Prior to each baseline visit, all participants ate a 5 day pre-study weight maintenance diet, the dietary characteristics of which are described above, with meals provided for home by the CTRC metabolic kitchen. Participants were asked to refrain from vigorous physical activity in the 24h
before each visit. As shown in Figure 4.2.2, procedures for fed and fasted baseline visits were identical, with the exception that on the fed visit participants were fed breakfast, lunch, dinner and a snack at standardized times. On a fasted visit participants were provided no food but had *ad libitum* access to water, non-caloric beverages and sugar-free chewing gum. On both visits, each morning blood collection at 7am was in the fasted state, after an overnight fast. Baseline visits were completed in random order (fed-fasted vs. fasted-fed) and were separated by 4 weeks to allow menstrual cycle consistency for women. On the night before the study participants checked at the CTRC at 7pm, completed eating questionnaires for the last week, and went to bed at 10pm. Participants stayed for 2 nights and 1 ½ days. Figure 4.2.2 gives an overview of the timing of tests conducted during baseline visits.

On day 1 of each baseline study participants were woken at 6:00am and immediately gave a saliva sample before getting out of bed. They gave another saliva sample at 6:30am after resting quietly in bed while resting metabolic rate (RMR) was assessed. After a 6:30 ECG for safety monitoring, a third saliva sample was collected at 7:00am. A nurse then drew blood, which was later used to assay glucose, insulin, pro-inflammatory cytokines and BDNF. Participants were then permitted to get up. They next completed the profile of mood states questionnaire (POMS), the perceived stress scale (PSS), and rated their hunger-satiety on visual-analogue scales (VAS). Following the questionnaires, participants completed the computerized cognitive test battery while seated in a quiet private hospital room. The cognitive test battery took approximately 20 minutes to complete. After completing the cognitive tests, participants were free to spend the remainder of the day as they chose, but were asked to remain within the hospital and wear an activity monitor. Vital signs were checked every 2 hours, and blood was drawn at 10:30am and at 2pm. Participants went to bed at 10pm.
On day 2 of each baseline visit procedures for the morning were the same as day 1 until completion of the cognitive tests. After completing the cognitive test battery participants underwent a frequently sampled intravenous glucose tolerance test (FSIVGTT) to determine insulin sensitivity. They were then fed a breakfast that provided approximately 20% of daily caloric needs, and rested for 15 minutes before completing the 90% VO\textsubscript{2} max stress test. Participants were then discharged from the hospital.

**Randomization to Intervention Group**

Sex-stratified randomization to either an intermittent fasting (IF) group or a standard dietary restriction (SDR) control group took place 1-2 weeks prior to commencing the dietary intervention.

**Study Diets**

In order to closely monitor dietary intake and composition, each participant’s food was provided by the CTRC metabolic kitchen. Dietary composition contained a macronutrient
content of 55% carbohydrates, 15% protein and 30% fat. To minimize the risk of micronutrient deficiency participants were given a multivitamin with iron to take every second day (the fed day for the IF group). Daily calorie distribution was 20% at breakfast, 30% at lunch, 40% at dinner and 10% for a snack. Baseline caloric intake for a weight maintenance diet was calculated to meet free-living energy requirements based on the formula \( [(372 + 23.9 \times \text{FFM}) \times 1.5] \). The accuracy of this estimate was tested during pre-baseline weight maintenance diets and adjusted to ensure weight maintenance. The calories required to maintain weight were used as the baseline caloric intake.

Participants on the IF diet were given a standard rotating menu for a weight maintenance diet, as well as 5-7 optional additional food modules for each meal (200 kcal each, macronutrient content similar to the rest of the diet) to allow the IF participant *ad libitum* access to food on their fed day. Provision of optional modules was adjusted as necessary throughout the intervention. Participants were given permission to eat as much as they wished from this food, but were not actively encouraged to eat all food provided. On fasted days participants were asked to consume only water and non-caloric beverages. Participants in the control group on the SDR diet received a standard rotating menu with a 400kcal/day deficit. All participants were instructed to maintain their usual levels of physical activity without change, however physical activity was not measured.

In order to minimize the risk of micronutrient deficiency, throughout the study both groups were given a multiple vitamin with iron (2 every other day, on feeding days, for the IF group in order to maximize absorption of fat soluble vitamins).

**Week 1 Visit**

To begin the dietary intervention, all participants were admitted to the CTRC at the beginning of their first week and remained in-patients for the entire week. For the first 4 days
they were given a day pass to go to work, but were asked to return to sleep at the CTRC to allow for continued safety monitoring. Metabolic testing similar to that conducted for the baseline visits began on day 5 of week 1. That is, on the 5th day (a fasting day for the IF group and a fed day for the SDR group) of the week, participants underwent a testing procedure identical to that already described for day 1 of the baseline visit. On the 6th day of week 1 (a fed day for both IF and SDR groups) the testing procedure was again the same. The 7th day of week 1 matched the procedures already described for day 2 of the baseline visit. As a result day 2 of the baseline fed visit and day 7 of the week 1 visit provide directly comparable measures, assessing both groups after a fed day. After completing the 90% VO2max stress test on the morning of the 7th day participants were discharged, and given meals and instructions to complete the remaining 7 weeks of intervention as closely monitored outpatients. They were instructed to maintain their usual level of physical in/activity.

**Intervention Period**

For the following 7 weeks all food for both groups was provided by the CTRC metabolic kitchen, so participants collected pre-prepared meals from the metabolic kitchen twice a week. In the IF group food collection took place after both a fed day and after a fasted day, and urine was collected for ketone measurement after the fasted day to measure dietary adherence. Weight was measured for all participants on each visit as another measure of adherence. For example, since the SDR group was expected to lose 6kg measured weight loss of <1kg/2wks was considered non-compliant, and participants were given options to assist adherence to the study diet. Once a week participants also completed a weekly eating questionnaire and POMS.

**Week 8 Visit**

During week 8 participants followed their respective diets. During the week a separate visit for final weight measurement and a repeat DXA were scheduled, giving the final post-
intervention weight. Participants were also admitted for an in-patient stay at the CTRC for days 5, 6 and 7 of week 8 to match the week 1 procedures described above. As a result day 7 of the week 8 visit provides measures directly comparable to day 7 of week 1. These match day 2 of the baseline fed visit, as each assesses outcomes after a fed day. At week 8 participants completed the questionnaires of eating disordered behavior (QEWP) and depression symptoms (CESD) comparable to those assessed at baseline. On day 7 participants ended their dietary intervention and were discharged with instructions to maintain a balanced low-fat diet as per the American Heart Association guidelines, but were free to choose their diet and levels of activity.

6 month Follow-Up

After 6 months participants were asked to return for a follow-up visit. They were scheduled for weight measurement and another DXA, as well as an overnight in-patient visit at the CTRC. Pre-visit dietary intake was not standardized. The testing conducted on the morning of the 6 month follow-up visit resembled day 2 of the baseline visits. Participants also completed the CESD, QEWP and a standard 7 day dietary recall diary. They were then fed a snack and discharged from the study.

4.2.5 Data Analysis

To control for baseline cognitive function and physiological function, repeated measures analysis of variance (ANOVA) of the effects of intervention group (IF or SDR) and time (baseline, week 8 and 6 month follow-up) were used for statistical comparisons in each cognitive domain (primary outcome). Between group differences at each time point were also calculated. Data were screened for outliers using frequency histograms, scatterplots and assessment. Outliers further than 3 standard deviations from the mean were assessed and analysis run both with and
without these variables to assess their influence on results. Normality was assessed for all cognitive domain scores. Cognitive domain scores were approximately normally distributed.

Secondary analyses examined effects of intervention group and time on adiposity (BMI, weight, and DXA-determined percentage of body fat and percentage trunk fat), glucose regulation (SI, glucose, insulin), HPA axis function (plasma cortisol morning peak, diurnal decline and cortisol response to exercise stress), pro-inflammatory cytokines (serum CRP, IL-6 and plasma TNF-α) and neurotrophic (plasma BDNF) activity, using similarly structured ANOVAs. For secondary outcomes and independent variables, normality, equality of variance and linearity of relationship to the cognitive outcomes assessed by residuals plots and scatterplots as part of regression diagnostics to prepare for regression with cognitive outcomes. Pairwise comparisons were performed using t tests when appropriate. Two-sided tests were used for all the comparisons, with a p value of 0.05 or less considered statistically significant and a p value of 0.01 or less considered highly statistically significant. All analyses were conducted with SPSS version 19 (IBM).

For each variable measured, two sets of change scores were calculated. First, scores after the 8 week intervention, taken at 7:00am on a fed day, were subtracted from values corresponding to 7:00am after a baseline fed day. Similarly, 6 month change from baseline was calculated as the difference between scores at 7am on the 6 month follow-up visit, subtracted from scores at 7:00am after a baseline fed day. While raw scores were used in analysis of variance, the change scores were used to assess correlation coefficients and in separate linear regressions to assess the association between change in cognitive domain (e.g. memory) and change in secondary outcome measures, including adiposity, diurnal cortisol, stimulated cortisol response (AUC), insulin sensitivity, inflammatory markers (TNF-α, CRP) and BDNF. Given the small sample size, principal covariates statistically considered for inclusion in the model included
age, education and change in measures of adiposity. While gender may influence outcome variables, such as change in HPA axis function (e.g. see (Baker et al., 2010)), in our sample of 26, 20 participants were female, reducing the power of adjustments for gender.

Diurnal cortisol was calculated using two measures. Peak morning cortisol, assessed at 6:30am of each study visit day, was used as the primary outcome for cortisol because it was available for each study visit, including the 6-month follow-up visit. Cortisol diurnal decline was also calculated by subtracting evening cortisol nadir, taken at 9:30pm, from morning peak half an hour after waking (6:30am) for study days were evening nadir was available. Stimulated cortisol response to the 90%V02max exercise stress test was calculated using cortisol output at each time point to generate area under the curve (AUC).

4.3 Results

4.3.1 Study Attrition

A total of 46 potential participants were screened for eligibility at the University of Colorado Hospital. Of these, 8 did not qualify for study entry (7 for medical reasons, including hyperthyroidism, uncontrolled hypertension and untreated bipolar disorder, and inability to manage a weight stable diet). The distribution of age, gender, ethnicity and education were similar to those in the remaining sample.

Thirty-eight remaining participants were considered eligible. However 5 declined to participate (for reasons of family or not enough time) and 2 withdrew shortly after enrolment (moving from Denver, new job responsibilities) Age, gender, education and ethnicity were similar to those found in the remaining sample. Hence only 31 completed the test fast, while 29 completed at least one test fast. Twenty-nine participants were randomized to the intervention. Of these 2 withdrew (did not like IVs, scheduling issues) and one person was dropped from the study (poor IV access, never started intervention). No systematic differences in age, gender,
education, ethnicity or BMI were detectable between the people who withdrew and those who chose to continue.

A total of 26 participants completed the intervention to its conclusion at 8 weeks. Of these, 14 were randomized the IF group, while 12 were randomized to the SDR group. Of the completers 19 returned for follow-up at 6-months.

In addition to attrition, some variables suffered loss of data at different time points. The reasons for the loss of data varied, but included technician error, laboratory error, or the inability to contact study personnel responsible for the data, as described above in the methods section. For this reason all tables and figures below indicate the actual number of participants’ data available for that measure at that time point if the full sample sizes was not available.

### 4.3.2 Sample Characteristics

Twenty-six obese (mean BMI=37.1, sd=5.3) adults aged 23-55 years completed the DRIFT study. Of these, 20 were women. Two participants self-identified as African American, 6 as Hispanic and 1 as other ethnicity. For one participant English was his second language, but he had completed a Ph.D. in English and was fluent in English. This participant completed the cognitive tests in Spanish. As can be seen in Table 4.3.1, some minor differences between the groups were apparent at baseline. Both African American participants were randomized to the IF dietary intervention group and more participants in the IF group reported being physically active at baseline than persons randomized to the SDR group. In addition the SDR group showed faster cognitive speed at baseline (p=0.049). Otherwise baseline characteristics of the two groups did not differ significantly.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>IF Group</th>
<th>SDR Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (n)</td>
<td>26</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.5 (9.0)</td>
<td>38.7 (9.7)</td>
<td>42.6 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Education (n)</td>
<td>26</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Completed college</td>
<td>15</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Some college or assoc.</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Completed HS or equiv.</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Gender (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
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<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Depression (CESD)</td>
<td>15.8 (4.3)</td>
<td>15.7 (5.6)</td>
<td>15.8 (2.3)</td>
<td>0.945</td>
</tr>
<tr>
<td>Eating Disorders (QEWP)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Self-reported physical activity</td>
<td>21</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Some activity</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Adiposity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>37.1 (5.3)</td>
<td>35.6 (4.2)</td>
<td>38.8 (6.0)</td>
<td>0.116</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>41.8 (5.7)</td>
<td>40.5 (6.2)</td>
<td>43.3 (4.8)</td>
<td>0.213</td>
</tr>
<tr>
<td>Trunk fat (%)</td>
<td>43.7 (5.7)</td>
<td>42.6 (6.7)</td>
<td>45.0 (4.2)</td>
<td>0.288</td>
</tr>
<tr>
<td><strong>HPA axis function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol morning peak (μg/dL) (n=14)</td>
<td>0.66 (.25)</td>
<td>0.63 (.27)</td>
<td>0.70 (.25)</td>
<td>0.657</td>
</tr>
<tr>
<td>Cortisol decline (μg/dL) (n=14)</td>
<td>0.60 (.29)</td>
<td>0.55 (.34)</td>
<td>0.66 (.23)</td>
<td>0.488</td>
</tr>
<tr>
<td>90% V02max cortisol AUC (n=22)</td>
<td>31 (24)</td>
<td>35 (31)</td>
<td>27 (13)</td>
<td>0.493</td>
</tr>
<tr>
<td><strong>Cognitive function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>97 (7.5)</td>
<td>98 (5.8)</td>
<td>95 (9.2)</td>
<td>0.447</td>
</tr>
<tr>
<td>Attention^</td>
<td>4.5 (3.7)</td>
<td>4.2 (3.9)</td>
<td>4.9 (3.7)</td>
<td>0.632</td>
</tr>
<tr>
<td>Reaction time^</td>
<td>620 (71)</td>
<td>615 (70)</td>
<td>624 (74)</td>
<td>0.760</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>56 (8.5)</td>
<td>57 (9.8)</td>
<td>55 (6.9)</td>
<td>0.453</td>
</tr>
<tr>
<td>Cognitive speed</td>
<td>184 (22.5)</td>
<td>192 (25.5)</td>
<td>175 (15.0)</td>
<td>0.049*</td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin sensitivity (SI)</td>
<td>1.62 (1.1)</td>
<td>1.90 (1.2)</td>
<td>1.29 (.96)</td>
<td>0.205</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>91.13 (7.82)</td>
<td>92.27 (7.16)</td>
<td>90.09 (8.21)</td>
<td>0.505</td>
</tr>
<tr>
<td>Insulin (μIU/mL)</td>
<td>18.71 (6.58)</td>
<td>15.58 (4.78)</td>
<td>21.83 (6.82)</td>
<td>0.521</td>
</tr>
<tr>
<td>BDNF (pg/mL)</td>
<td>20253 (5197)</td>
<td>19130 (5569)</td>
<td>21469 (4689)</td>
<td>0.270</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>33.49 (13.62)</td>
<td>33.12 (12.38)</td>
<td>33.87 (15.31)</td>
<td>0.896</td>
</tr>
</tbody>
</table>

Note: * Significant at p=0.05. ^ Lower scores represent better function.
4.3.3 Safety

A safety monitor (DSMP) followed the DRIFT study closely. Four minor adverse events were reported to the safety officer (headaches). One person experienced DVT during the course of the study, but it was determined that this was not related to study involvement. One person had cholecystectomy but not gallstones, which was also unlikely to be caused by study involvement.

4.3.4 Dietary Adherence

All participants were asked to remain as in-patients in the CTRC unit in the first week of the intervention to ensure adherence to the diet and to monitor for safety. After their discharge, adherence over the ensuing 7 weeks of the intervention was monitored on a bi-weekly basis in a number of ways. All meals were provided to both groups, and participants were asked to return uneaten food, which was weighed as a measure of compliance with the diet. All participants were weighed at these visits, and urine samples were also collected from participants in the IF group after a fasting day to test for ketones. Based on the expected weight loss of 6kg in the CR group and 6-11kg in the IF group a weight loss < 1kg/2weeks was considered non-compliant for either group. Participants also completed a weekly eating questionnaire, which was checked for evidence of dietary non-compliance. Participants who were non-compliant were encouraged to work collaboratively with the study team to develop strategies that would increase the tolerability of the diet, and/or asked to work with the study team to develop minor adjustments to the diet to optimize adherence. While two participants did not demonstrate the anticipated weight loss by the end of the study period (both IF, stated reason was a felt need to consume all the food provided by the metabolic kitchen, which was made available in excess of caloric needs for the IF group), no participants were considered non-compliant, and no participants were
dropped from the study for reasons of non-adherence to the diet. In addition no participants withdrew from the intervention because of difficulty tolerating either the diet.

4.3.5 Acute Effects of Fasting

Acute effects of a single short-term (36h) fast on obese adults were assessed with the full sample, before randomization (n=26). It was not possible to determine whether participants found fasting psychologically stressful due to the large number of missing questionnaires for the baseline visits (technician error, POMS and PSS not administered or misplaced).

However short-term fasting did produce mild but significant reductions in glucose consistent with mild metabolic stress. As can be seen in Table 4.3.2 below, serum glucose and insulin were significantly lower after a day of fasting than after a fed day (p<0.001), but insulin sensitivity decreased (p=0.010). Cortisol morning peak was also significantly lower after a fasted day than after a fed day (p=0.002). Short-term fasting did not have any significant effects on any cognitive domains. Most other physiological markers were unchanged by acute fasting.

To determine whether regular exposure to short-term fasting produces habituation to the effects of fasting, the effect of a matched 36-hour fasting day on in week 8 (day 5) was assessed for participants in the IF group only. Fasting response was not assessed for the SDR group, as they did not undergo fasting at 8 weeks. Within group comparison of the baseline and week 8 fasts for the 14 participants in the IF group indicated that the decrease in glucose after a fasting day was the same at both times (mean change=0.000, p=1.00). However the morning peak cortisol after a fast was significantly higher after 8 weeks of the IF intervention than that found after a baseline fast (mean change =0.69 μg/dL, sd=0.32, p=0.01, n=8).
Table 4.3.2. Effects of an acute 36h fast at baseline on all participants before randomization (n=26). Measures were collected at 7am the following day.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>After a fed day</th>
<th>After 36h fast</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (sd)</td>
<td>Mean (sd)</td>
<td></td>
</tr>
<tr>
<td><strong>Physiological stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dL) (n=23)</td>
<td>91.1 (7.6)</td>
<td>84.2 (5.3)</td>
<td>.000**</td>
</tr>
<tr>
<td>Insulin (μIU/mL) (n=23)</td>
<td>18.9 (6.7)</td>
<td>12.0 (4.5)</td>
<td>.000**</td>
</tr>
<tr>
<td>Cortisol morning peak (μg/dL) (n=14)</td>
<td>.66 (.25)</td>
<td>.46 (.20)</td>
<td>.002**</td>
</tr>
<tr>
<td><strong>Psychological stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived stress (PSS)</td>
<td>Insufficient n</td>
<td>Insufficient n</td>
<td>N/A</td>
</tr>
<tr>
<td>Tension/anxiety (POMS)</td>
<td>Insufficient n</td>
<td>Insufficient n</td>
<td>N/A</td>
</tr>
<tr>
<td>Mood score (POMS)</td>
<td>Insufficient n</td>
<td>Insufficient n</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Cognitive function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory (n=25)</td>
<td>96.6 (7.5)</td>
<td>97.0 (11.1)</td>
<td>.792</td>
</tr>
<tr>
<td>Attention^ (n=24)</td>
<td>4.5 (3.7)</td>
<td>7.8 (10.5)</td>
<td>.074</td>
</tr>
<tr>
<td>Reaction time^ (n=25)</td>
<td>620 (70.7)</td>
<td>609 (58.2)</td>
<td>.318</td>
</tr>
<tr>
<td>Cognitive flexibility (n=25)</td>
<td>56 (8.5)</td>
<td>53 (15.4)</td>
<td>.111</td>
</tr>
<tr>
<td>Cognitive speed (n=25)</td>
<td>184 (22.5)</td>
<td>181 (19.7)</td>
<td>.411</td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin sensitivity (SI) (n=24)</td>
<td>1.62 (1.15)</td>
<td>1.24 (1.09)</td>
<td>.010*</td>
</tr>
<tr>
<td>BDNF (pg/mL)</td>
<td>20126 (5270)</td>
<td>20649 (6054)</td>
<td>.728</td>
</tr>
<tr>
<td><strong>HPA axis function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol decline (μg/dL) (n=14)</td>
<td>.597 (.29)</td>
<td>.472 (.25)</td>
<td>.306</td>
</tr>
<tr>
<td>90% VO2max cortisol AUC (n=22)</td>
<td>31.14 (24.4)</td>
<td>29.50 (27.1)</td>
<td>.566</td>
</tr>
</tbody>
</table>

Notes: ^ lower scores indicate better performance. * statistically significant, p<0.05. ** highly statistically significant, p<0.01.

All 26 participants participated in both baseline fed and baseline fasted visits. Where data were missing for specific variables the actual sample size used in the calculation is indicated above.
4.3.6 Effects of IF on Body Weight and Composition

![Box plots showing weight change by group.](image)

**Figure 4.3.1. Eight week change in body weight by group (kg).**

After 8 weeks of dietary restriction both the IF and SDR groups lost significant amounts of weight ($p<0.05$), losing an average of 6.5% (sd=5.0%), and 5.75% (sd=2.5%) of body weight respectively. As seen in Table 4.3.3 below, the difference between the groups’ weight loss at 8 weeks was not statistically significant. However data screening revealed that although all other participants lost weight by 8 weeks, one participant in the IF group gained weight by the end of the intervention (6.95kg), and another in the same group maintained her baseline weight. This is depicted in Figure 4.3.1. Both participants were African American. After excluding these two participants from the comparison of weight change, mean weight loss in the IF group was 8.0%
(sd=3.41), though the difference in weight loss between the two groups was not statistically significance (p=0.082). Since the participant who gained weight did not return for 6-month follow-up this person was automatically excluded from analysis of variance and regression across the three key study times. The person who maintained her weight was retained in the analyses.

![Figure 4.3.2. Eight week percent weight change for each participant.](image)

Analysis of variance indicated that both groups decreased their proportion of fat mass over time (p=0.01), with a trend for between-group differences (p=0.056). As shown in Figure 4.3.3, participants in the IF group continued to lose weight after the intervention, while the SDR group did not. However the interaction did not reach statistical significance (p=0.071). A 6-month between group difference in weight lost is apparent (Table 4.3.5).
While both groups lost trunk fat during the 8 week intervention, analysis of variance revealed a significant interaction between intervention group and time (p=0.008). As shown in Figure 4.3.4, participants in the IF group continued to lose trunk fat after the end of the intervention, while the SDR group did not. The 6 month change in trunk fat showed a strong
correlation with 6-month change in BMI (0.65, p=0.002) and fat mass (R=0.79, p=0.000). As
noted in Table 4.3.3, change scores used in correlations and regressions were calculated by
subtracting 6 month weight from baseline weight. As a result, positive change scores in analyses
represent a better weight outcome (i.e. more weight lost).
Table 4.3.3. Eight week post-intervention group differences in weight and cognitive function.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IF Group mean (sd)</th>
<th>SDR Group mean (sd)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size~</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>Adiposity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in weight (%)</td>
<td>6.50 (5.03)</td>
<td>5.75 (2.56)</td>
<td>0.65</td>
</tr>
<tr>
<td>BMI</td>
<td>33.43 (4.70)</td>
<td>36.75 (5.80)</td>
<td>0.12</td>
</tr>
<tr>
<td>Change in BMI</td>
<td>-2.29 (1.73)</td>
<td>-2.25 (1.22)</td>
<td>0.95</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>39.57 (6.51)</td>
<td>42.42 (5.07)</td>
<td>0.22</td>
</tr>
<tr>
<td>Change in % fat mass</td>
<td>-1.07 (1.27)</td>
<td>-1.00 (1.13)</td>
<td>0.63</td>
</tr>
<tr>
<td>Trunk fat (%)</td>
<td>41.29 (7.08)</td>
<td>44.00 (4.57)</td>
<td>0.25</td>
</tr>
<tr>
<td>Change in % trunk fat</td>
<td>-10.07 (7.74)</td>
<td>-8.58 (5.66)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Cognitive function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>98.00 (12.25)</td>
<td>95.67 (10.52)</td>
<td>0.61</td>
</tr>
<tr>
<td>Change in memory</td>
<td>.00 (11.17)</td>
<td>.33 (8.08)</td>
<td>0.93</td>
</tr>
<tr>
<td>Attention ^</td>
<td>5.50 (3.59)</td>
<td>6.08 (5.66)</td>
<td>0.75</td>
</tr>
<tr>
<td>Change in attention</td>
<td>-1.62 (4.61)</td>
<td>-1.63 (5.26)</td>
<td>0.99</td>
</tr>
<tr>
<td>Reaction time ^</td>
<td>620.36 (59.51)</td>
<td>632.08 (85.49)</td>
<td>0.69</td>
</tr>
<tr>
<td>Change in reaction time</td>
<td>-12.15 (79.78)</td>
<td>-7.29 (64.89)</td>
<td>0.87</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>57.93 (7.44)</td>
<td>57.58 (7.59)</td>
<td>0.91</td>
</tr>
<tr>
<td>Change in cognitive flexibility</td>
<td>.38 (9.75)</td>
<td>-2.50 (9.59)</td>
<td>0.46</td>
</tr>
<tr>
<td>Cognitive speed</td>
<td>193.00 (19.86)</td>
<td>174.83 (20.23)</td>
<td>0.03</td>
</tr>
<tr>
<td>Change in cognitive speed</td>
<td>0.4615 (14.08)</td>
<td>0.333 (11.86)</td>
<td>0.84</td>
</tr>
<tr>
<td>Depression (CESD)</td>
<td>8.15 (6.44) n=13</td>
<td>5.91 (3.91) n=11</td>
<td>0.32</td>
</tr>
<tr>
<td>Change in depression</td>
<td>7.54 (5.61)</td>
<td>9.82 (3.28)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: ^ lower scores indicate better performance. *Statistically significant at p<0.05. Change scores calculated as change from baseline (baseline – 8 weeks).

~All 26 participants participated in the baseline and 8 week study visits. Where data were missing for specific variables the actual sample size used in the calculation is indicated above. Sample sizes are only provided where the sample differed from the full sample.
### Table 4.3.4. Eight week post-intervention group differences in biomarkers.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IF Group mean (sd)</th>
<th>SDR Group mean (sd)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>HPA axis function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol morning peak (μg/dL)</td>
<td>0.59 (.36) n=13</td>
<td>0.65 (.28) n=10</td>
<td>0.66</td>
</tr>
<tr>
<td>Change in cortisol morning peak</td>
<td>-.03 (0.45) n=8</td>
<td>.09 (.50) n=8</td>
<td>0.64</td>
</tr>
<tr>
<td>Cortisol decline (μg/dL)</td>
<td>0.56 (0.33) n=12</td>
<td>0.64 (0.317) n=10</td>
<td>0.55</td>
</tr>
<tr>
<td>Change in cortisol decline (μg/dL)</td>
<td>-0.08 (0.16)</td>
<td>0.08 (0.10) n=6</td>
<td>0.059</td>
</tr>
<tr>
<td>90% VO2max cortisol AUC</td>
<td>28.56 (26.84) n=9</td>
<td>15.00 (7.07) n=9</td>
<td>0.16</td>
</tr>
<tr>
<td>Change in 90% VO2max cort AUC</td>
<td>-1.44 (21.83) n=9</td>
<td>13.56 (12.48) n=9</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin sensitivity (SI)</td>
<td>2.04 (1.42) n=12</td>
<td>1.55 (.756) n=10</td>
<td>0.34</td>
</tr>
<tr>
<td>Change in Insulin Sensitivity</td>
<td>-.17 (.54) n=12</td>
<td>-.21 (.67) n=10</td>
<td>0.88</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>93.08 (5.52)</td>
<td>96.50 (8.63)</td>
<td>0.26</td>
</tr>
<tr>
<td>Change in glucose</td>
<td>-1.22 (6.30) n=9</td>
<td>-6.42 (8.61)</td>
<td>0.14</td>
</tr>
<tr>
<td>Insulin (μIU/mL)</td>
<td>15.42 (5.99)</td>
<td>17.17 (7.09)</td>
<td>0.521</td>
</tr>
<tr>
<td>Change in insulin</td>
<td>-.80 (5.49)</td>
<td>4.67 (6.67)</td>
<td>0.05</td>
</tr>
<tr>
<td>BDNF (pg/mL)</td>
<td>18127.79 (7410.36)</td>
<td>20343.75 (5825.80)</td>
<td>0.411</td>
</tr>
<tr>
<td>Change in BDNF</td>
<td>1177.08 (9522.81)</td>
<td>1125.5 (6020.05)</td>
<td>0.99</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>27.23 (13.48)</td>
<td>25.13 (12.89)</td>
<td>0.700</td>
</tr>
<tr>
<td>Change in leptin</td>
<td>6.28 (7.26) n=10</td>
<td>8.73 (6.10)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Notes: ^ lower scores indicate better performance. *Statistically significant at p<0.05. Change scores calculated as change from baseline (baseline – 8 weeks).

~All 26 participants participated in the baseline and 8 week study visits. Where data were missing for specific variables the actual sample size used in the calculation is indicated above. Sample sizes are only provided where the sample differed from the full sample.
4.3.7 Effects of IF on Cognitive Function

To test the hypothesis that IF improves memory function in obese humans, effects of IF on cognitive function were measured. After the 8 week interventions, neither group showed significant changes from baseline in any cognitive domains. However by the 6 month follow-up, the IF group showed significantly greater improvements in memory relative to baseline performance than the SDR group and analysis of variance indicated a significant main effect of group \((p=0.013)\). No other cognitive domains showed significant change at the 6-month follow-up. The changes in memory performance are shown in Figure 4.3.5. For the CNS Vital Signs cognitive test battery, higher memory scores represent better performance.

![Image: Mean memory scores by time and intervention group.](image)

**Figure 4.3.5.** Mean memory scores by time and intervention group.

The effects of adjusting for weight or adiposity were assessed to determine whether changes in cognitive function were mediated by changes in weight or fat distribution. The effect of intervention group on 6 month change in memory remained significant after controlling for 6-
month change in BMI (p=0.013) or after controlling for 6 month change in percentage fat mass (p=0.021). However after controlling for 6 month change in percentage trunk fat the between-group differences in memory were no longer statistically significant (p=0.088). As described above, there was an interaction between group and time for trunk fat, such that participants in the IF group continued to lose trunk fat after the intervention, while the SDR group did not. Linear regression showed that change in trunk fat was a significant predictor of change in memory for the IF group (β=0.828, p=0.022) but not the SDR group (p=0.768).

4.3.8 Effects of IF on Glucose Regulation

Effects of IF on glucose regulation were explored to investigate whether change in glucose regulation might mediate the effect of IF on memory. As can be seen in Figure 4.3.6, analysis of variance showed a trend for improved insulin sensitivity in the IF group at 6 months that was not apparent for the SDR controls. The trend did not reach statistical significance even though the two groups were different at 6 months. Insulin sensitivity at 6 months was significantly associated with 6 month change in insulin (R=-0.676, p=0.011, n=13), but not associated with change in glucose, or changes in weight. Simple linear regression models showed that there was no association between 6-month change in memory and change in insulin sensitivity, glucose, or insulin.
4.3.9 Effects of IF on BDNF

Effects of IF on BDNF were explored to investigate whether change in BDNF might mediate the effect of IF on memory. Analysis of variance indicated a significant time by group interaction effect for BDNF. As can be seen in Figure 4.3.6, BDNF did not change significantly for either group by the end of the 8 week intervention. However participants in the IF group showed increases in BDNF at 6-month follow-up (p=0.07), while the SDR group tended towards a decrease in BDNF. In separate models the interaction remained significant after controlling for 6 month change in BMI (p=0.010), or 6 month change in percent fat mass (p=0.011). However the interaction was no longer significant after controlling for change in percentage trunk fat (p=0.056). Controlling for change in insulin sensitivity increased the significance of the interaction (p=0.004), and remained significant after controlling for change in glucose (p=0.040).

Figure 4.3.6. Mean insulin sensitivity (SI) by time and group.
Increased BDNF was associated with reductions in glucose, but the association was no longer significant after controlling for intervention group.

The timing and direction of the changes in BDNF reflected those found for memory. However no evidence was available that BDNF mediated the effect of IF on memory function. Simple linear regression models showed that there was no association between 6-month change in memory and change in BDNF.

![Figure 4.3.7. Mean BDNF by time and group (pg/mL).](image)

4.3.10 Effects of IF on HPA Axis Function

There were insufficient data to test whether HPA axis function mediate the 6 month change in memory. Due to circumstances beyond our control, some cortisol data could not be retrieved for statistical analysis. With the sub-set of data available, only a relatively small number of participants’ data were available across all of the three time points. Repeated measures analysis of variance therefore included only 5 participants from the IF group and 4
participants from the SDR group, and did not show statistical significance. Between-group comparisons at 8 weeks showed no differences in peak morning cortisol or change in peak cortisol at 8 weeks.

Between group comparison of change in stimulated cortisol output in response to exercise stress was not significant (p=0.092). These results did not differ after excluding participants who gained or maintained weight.

However after excluding participants in the IF group who either gained or maintained their weight (n=2), the IF group showed significant increases in cortisol decline (morning peak-evening nadir) after the 8 week intervention, relative to the SDR group (p=0.039, n=13). When the IF participants who did not lose weight were included the comparison approached statistical significance (p=0.053, n=15). Cortisol decline at 8 weeks predicted memory scores the following day (β=0.451, p=0.035, n=22), but regression of changes from baseline did not reach significance (n=12). Six month changes in cortisol decline could not be assessed since full 24h cortisol was not collected at 6 month follow-up.

There were no significant between-group differences in other measures of HPA axis function at 6-month follow-up. However 6-month change in peak morning cortisol from baseline to 6-months was strongly correlated with 6 month change in glucose (R=0.914, p=0.000, n=7), though not with change in insulin or insulin sensitivity. Although correlation coefficients between peak morning cortisol and change in percent trunk fat and percent fat mass were high (0.51 and 0.62 respectively) they did not reach statistical significance in a sample size of 7. With very few participants with cognitive and cortisol data at both baseline and 6 months (n=5), change in peak cortisol was not a significant predictor of memory (p=0.099). However there was a trend for an association between higher morning cortisol and better same-day memory scores at the 6 month visit ($R^2=0.162$, $\beta=-0.464$, p=0.061, n=17).
4.3.11 Effects of IF on Pro-Inflammatory Cytokines

There were insufficient data to test whether changes in inflammatory markers had the potential to partially mediate the 6 month change in memory. Data for inflammatory markers were unreliable due to systematic inter-assay differences between the results obtained by different laboratory personnel, making interpretation of these data difficult. The data for TNF-α suggest that both groups showed increased TNF-α at 8 weeks, with no significant between-group differences. At 6 month follow-up TNF in the IF group appears to decline towards baseline, while the SDR group continued to rise. However calculated values systematically increased across different assays, and later study time points were more likely to be done on later assays significant variability in the assays for CRP and IL-6 rendered these data uninterpretable.

4.3.12 Effects of IF on Leptin

Effects of IF on leptin were explored to investigate whether change in leptin might partially mediate the effect of IF on memory. As shown in Figure 4.3.8 there were no significant between-group differences in leptin at any time point. However both groups showed a highly significant decrease in leptin at 8 weeks (p=0.000). Simple linear regression showed that change in trunk fat and change in fat mass were significant predictors of this 8 week change in leptin (R²=16.5%, β=-0.452, SE=0.233, p=0.035 and R²=18.8%, β=-0.476, SE=0.192, p=0.025 respectively). As with other studies, consistent gender differences in leptin levels were observed. Women had significantly higher levels of leptin than men.

Change in leptin did not predict change in memory scores. However leptin at 8 weeks did predict memory at 8 weeks, accounting for 17.1% of the variance in memory score at that time (β=-0.455, SE=0.168, p=0.026). Similarly leptin at baseline predicted memory at baseline
(accounted for 8.5% of variance in memory, (β=-0.353, SE=0.107, p=0.000). Leptin at 6 months did not predict memory at that time.

Figure 4.3.8. Mean leptin by time and group (ng/mL).
### Table 4.3.5. Between group differences 6 months after the end of the interventions.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IF Group Mean (sd)</th>
<th>SDR Group Mean (sd)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size**</td>
<td>n = 10</td>
<td>n = 10</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>31.70 (2.79)</td>
<td>38.50 (6.80)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Change in BMI</td>
<td>2.00 (2.21)</td>
<td>0.70 (1.57)</td>
<td>0.147</td>
</tr>
<tr>
<td>Trunk fat (%)</td>
<td>38.60 (.95)</td>
<td>45.70 (4.90)</td>
<td>0.441</td>
</tr>
<tr>
<td>Change in % trunk fat</td>
<td>2.40 (1.71)</td>
<td>0.00 (1.8)</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

#### HPA axis function

- Cortisol morning peak (μg/dL): IF 0.50 (0.24) \(n=9\), SDR 0.48740 (0.25) \(n=10\), \(p=0.671\)
- Change in cortisol morning peak: IF 0.23 (0.32) \(n=5\), SDR 0.07 (0.07) \(n=4\), \(p=0.376\)
- 90% VO2max cortisol AUC: IF 21.40 (15.32) \(n=5\), SDR 15.20 (6.83) \(n=5\), \(p=0.367\)
- Change in 90% VO2max: IF 8.4 (16.23) \(n=5\), SDR 10.40 (11.71) \(n=5\), \(p=0.829\)

#### Cognitive function

- Memory: IF 104.75 (5.26) \(n=8\), SDR 93.80 (8.07) \(n=10\), \(p=0.450\)
- Change in memory: IF 7.29 (8.32) \(n=7\), SDR 0.9 (8.79) \(n=10\), \(p=0.006*\)
- Attention\(^\wedge\): IF 3.25 (3.85) \(n=8\), SDR 6.00 (3.43) \(n=9\), \(p=0.648\)
- Change in attention: IF -.43 (3.65) \(n=7\), SDR .38 (4.03) \(n=8\), \(p=0.694\)
- Reaction time\(^\wedge\): IF 592.13 (55.85) \(n=8\), SDR 602.44 (65.85) \(n=9\), \(p=0.841\)
- Change in reaction time: IF 7.00 (72.78) \(n=7\), SDR 18.89 (46.83) \(n=9\), \(p=0.697\)
- Cognitive flexibility: IF 63.00 (7.84) \(n=8\), SDR 51.20 (15.84) \(n=10\), \(p=0.299\)
- Change in cognitive flexibility: IF -1.43 (5.50) \(n=7\), SDR 3.20 (17.86) \(n=10\), \(p=0.520\)
- Cognitive speed: IF 193.63 (22.14) \(n=8\), SDR 179.56 (17.47) \(n=9\), \(p=0.418\)
- Change in cognitive speed: IF 9.43 (9.03) \(n=7\), SDR -4.00 (9.03) \(n=9\), \(p=0.021\)

#### Biomarkers

- Insulin sensitivity (SI): IF 3.04 (3.84) \(n=7\), SDR 1.31 (.60) \(n=9\), \(p=0.046*\)
- Change in insulin sensitivity: IF -0.97 (2.27) \(n=7\), SDR 0.55 (0.76) \(n=9\), \(p=0.218\)
- Glucose (mg/dL): IF 85.63 (5.85), SDR 93.30 (6.33), \(p=0.018*\)
- Change in glucose: IF 2.17 (7.08) \(n=6\), SDR -2.90 (4.28) \(n=10\), \(p=0.093\)
- Insulin (μIU/mL): IF 12.86 (5.38), SDR 16.80 (4.27), \(p=0.121\)
- Change in insulin: IF 1.17 (2.87) \(n=7\), SDR 5.70 (6.07) \(n=10\), \(p=0.130\)
- BDNF (pg/mL): IF 26401.11 (6170.05) \(n=9\), SDR 18498.60 (5514.60) \(n=10\), \(p=0.613\)
- Change in BDNF: IF -6970.62 (6790.56) \(n=8\), SDR 3332.90 (7313.31) \(n=10\), \(p=0.007*\)
- Leptin (ng/mL): IF 27.85 (15.16) \(n=8\), SDR 33.23 (18.17) \(n=10\), \(p=0.512\)
- Change in leptin: IF 5.47 (16.53) \(n=7\), SDR 1.21 (4.90) \(n=10\), \(p=0.449\)

Notes: \(^\wedge\) lower scores indicate better performance. * statistically significant at \(p<0.05\); ** statistically significant at \(p<0.001\). Change scores are calculated as change from baseline (baseline – 6 months).

\(\sim\)20 participants returned for the 6-month follow-up visits. Where data were missing for specific variables the actual sample size used in the calculation for that variable is indicated above.
4.4 Discussion

As hypothesized, IF produced significantly greater effects on the cognitive function of obese adults than standard dietary restriction. The observed changes in cognitive function were specific to improvements in memory, a finding consistent with the effects of IF in animals (Anson et al, 2003). Interestingly, these effects on memory were not apparent at the end of the 8 week intervention. Instead memory effects appeared 6 months after the interventions concluded. It is therefore significant that by 6 months the IF group showed significantly greater reductions in trunk fat than the SDR group. This reduction in trunk fat partially mediated the change in memory performance observed at 6-months. Both dietary interventions significantly reduced global adiposity, as indicated by changes in BMI, weight and fat mass; however between-group differences were not statistically significant at 8 weeks or 6 months and were not related to change in memory scores.

While these findings do not prove that central obesity was the cause of cognitive deficits in study participants, the results are consistent with the hypothesis that factors specifically related to central adiposity affect human memory function. This is consistent with epidemiological evidence of an association between central obesity in midlife and later cognitive decline (Cereda, Sacchi, & Malavazos, 2009; West & Haan, 2009; Whitmer et al., 2008), and argues for more widespread inclusion of measures of central obesity in future epidemiological and intervention studies. Several plausible mechanisms link central obesity to cognitive decline and dementia. Excess central adipose tissue can contribute to glucose dysregulation, low-grade systemic inflammation (Barzilay et al, 2001), and HPA axis dysregulation (Bjorntorp & Rosmond, 2000), each of which may play a causal role in the pathophysiology of Alzheimer’s disease (Craft, 2005, 2007; De Leon et al., 1997; Lupien et al., 1999). However as previously discussed, many research studies to date have used BMI as their sole measure of adiposity when testing for an
association between obesity and cognitive function. However BMI gives a poor reflection of body composition, and cannot be used assess any specific risks attributable to central obesity.

This study did not collect data that would determine why participants in the IF group, but not the SDR group, continued to lose weight after the conclusion of the intervention. However there are a number of possible explanations. Many possible factors could explain these differences, but no additional measures were added to the 6-month follow-up that could be used to give clear answers. All measures at the 6-month follow-up mirrored those of the preceding visits. For example it would have been useful to collect data on participant behavior in the intervening time, including dietary patterns and rates of physical activity. Among the possible explanations for the differences, it is possible that participants in the IF group continued to engage in some form of regular fasting. No systematic data were collected on post-intervention dietary practices, however the experience of IF and the behavior change skills acquired during the intervention period would have been quite different to those of the SDR group. Anecdotally, some people find IF more simple and easy to follow than calorie restriction. Different post-intervention dietary behavior would account for the additional weight loss in the IF group observed at the 6 month follow-up, but it would not fully explain the between-group differences in fat distribution, for the IF group lost significantly more trunk fat than the SDR group.

Another possibility for the difference in fat distribution between the groups at 6 months is that IF produced different neuroendocrine changes than SDR. It may have had differential effects in improving metabolic efficiency, or improving regulation of a wide variety of hormones involved in energy balance. In addition, IF can be considered a form of repeated mild metabolic stress. The hormesis hypothesis (Calabrese & Baldwin, 2001; Mattson & Calabrese, 2010), suggests that this mild stress can be beneficial, and contributes to the beneficial effects of IF by
improving function of stress response systems and resilience against stress (Martin et al., 2006). According to this hypothesis short-term fasting is psychologically and metabolically stressful. Consistent with this, we found that acute (36h) fasting induced mild decreases in glucose. As expected, the fasting-induced change in glucose was significantly correlated with changes in cortisol, however the direction of the association was opposite to that hypothesized. The mild reductions in glucose observed after fasting did not appear to provoke a counter-regulatory increase in cortisol in this sample. Instead reductions in glucose were associated with decreased morning cortisol peak. The reason for this counter-intuitive response to fasting at baseline is not clear. It may reflect a dysregulated baseline state, for the cortisol response to a fast changed after 8 weeks. Eight week changes in fasting response could only be assessed within the IF group, since they alone underwent fasting at that time. Within this group, participants’ glucose response to a short-term 36h fast remained the same as baseline, suggesting that a short-term fast continued to represent a mild metabolic stressor throughout the study. However after 8 weeks of IF, participants’ morning cortisol peak after a fasted day was significantly higher than baseline fasting response (p=0.001), even though peak morning cortisol after a fed day remained unchanged. Hence participants mounted a stronger cortisol response to an acute fast after 8 weeks of IF. A strong cortisol response to fasting may be an adaptive, healthy counter-regulatory response (Bergendahl, Iranmanesh, Mulligan, & Veldhuis, 2000). In animal research, the APP mutant mouse model of AD, which shows HPA axis abnormalities and excess amyloid deposition in the brain, was apparently unable to mount an adaptive response to fasting when placed on an IF diet, and died within weeks of starting the diet (Pedersen et al., 1999). A healthy adaptation to fasting may therefore be an important to the effects of IF, and this finding in humans is consistent with an intervention-related change in the HPA axis response to fasting. Since the effect could not be compared to the control group it is not possible to determine if it
was specific to the IF intervention. This study is the first to assess the effects of IF on human HPA axis function using rigorous standardized measures. Although only a partial dataset was finally available for most measures of HPA axis function, trends within the available data were consistent with intervention-related changes in HPA axis function. These included a tendency for response to the exercise stress test to increase for the IF but not SDR group, greater increase in diurnal cortisol decline after the 8 week intervention in the IF group \( (p=0.039, n=13) \) that occurred before significant between-group differences in trunk fat were apparent. Since both groups lost a similar amount of weight and trunk fat by 8 weeks, the differences are unlikely to be attributable to reductions in adiposity alone. Hence it may provide some evidence to support the idea that altered neuroendocrine effects contributed to the ongoing IF group.

The results of this study were also consistent with existing evidence surrounding mechanisms that could mediate an effect of obesity on neurocognitive health. As hypothesized, IF produced significantly greater improvements in BDNF than the SDR control, and these differences remained after adjusting for weight change, percent fat mass change or change in BMI. However controlling for change in trunk fat attenuated the intervention-related effect on BDNF and halved the effect size, though the effect still approached significance \( (p=0.056) \). Interestingly, change in BDNF was not associated with change in memory, although both were improved in the IF group at 6 month follow-up, and both effects appeared to be partially mediated by changes in trunk fat. Participants varied in whether they improved on memory or BDNF, and these did not co-vary together. It is unlikely that changes in plasma BDNF contributed causally to improvements in memory in this study. Other human research has indicated low BDNF in persons who are obese or who have dementia (Cole & Frautschy, 2007; Vaynman & Gomez-Pinilla, 2006), and higher levels of BDNF are associated with better learning and memory in animals (neural BDNF; e.g. (Diogenes et al., 2007) and humans (plasma BDNF;
(Alonso et al., 2002; Komulainen et al., 2008). However BDNF is thought to be a neuroprotective factor that is upregulated in response to potential neuronal stress, injury, or inflammation (Yasutake et al., 2006a). Johnson et al. (2007) found that modified IF led to decreased BDNF in obese persons with asthma, and that these reductions corresponded to reductions in inflammation and asthma symptoms. It is possible that part of our sample entered the study with heightened BDNF in response to inflammation or other stressors, and that BDNF decreased for this sub-group as inflammation decreased. Since the pro-inflammatory cytokine data collected as part of this study were not reliable, it is not possible to test this possibility, and future research should explore this further. It does, however, highlight an issue with BDNF testing and interpretation. As currently conceptualized, high BDNF can represent either the good health that comes with a neuroprotective factor, or the poor health that requires an adaptive protective response. Other factors are therefore needed to aide the interpretation of BDNF results. In this study, increases in BDNF were related to reductions in glucose. Since the brain relies on glucose for fuel, BDNF may have been mobilized as part of a protective response against the threat of glucose deprivation. Only the IF group had recurring periods of glucose deprivation. The exposure to repeated glucose deprivation may have shaped the between-group differences in BDNF, however further research with larger sample sizes is needed to parse out these effects from those attributable to intervention group or change in trunk fat.

Extensive mediation modeling of the effects of changes in BDNF, glucose regulation, inflammatory cytokines or HPA axis function on memory were beyond the power of this exploratory study. However trends in the data are consistent with beneficial effects of IF on central adiposity, glucose regulation, HPA axis function and trophic factors. Each of these factors is independently implicated in the pathophysiology of age-related cognitive decline and dementia. Given the animal literature supporting significant neuroprotective effects for IF,
including slower cognitive aging, the effects of IF on these potential mediating mechanisms should be explored further.

In this first test of the effects of intermittent fasting on human cognitive function it is worth noting that IF did not have detrimental effects on any cognitive domain measured, including memory, attention, cognitive flexibility, cognitive speed and reaction time. Similarly, supervised weight loss by standard dietary restriction did not result in cognitive deficits. Before contemplating weight loss as a potential solution any increased risk of cognitive decline and dementia in obese adults, it is important to establish the safety and efficacy of weight loss. The direction of the effect is important, particularly in light of the association between weight loss and adverse cognitive outcomes in some older adults (Stewart et al., 2005; Wirth et al., 2007), adverse effects of Ramadan fasting (Roky et al., 2003; Roky et al., 2004; Roky et al., 2000), and some findings of worse cognitive function after unsupported dieting, these results are potentially important (Green & Rogers, 1995, 1998; Green, Rogers, Elliman, & Gatenby, 1994).

Results of this study suggest that it is safe to test the effects of IF more widely on the human population, and that participants in such studies may experience significant health benefits that endure beyond the conclusion of the study. Follow-up research in populations at increased risk of cognitive decline, including persons with Mild Cognitive Impairment (MCI), Type 2 diabetes mellitus or the Metabolic syndrome, or persons with HPA axis dysregulation, should be conducted to determine whether IF may reduce risk of cognitive decline. Such research should include sample sizes sufficient to provide the power to detect significant changes in HPA axis function, to determine whether beneficial effects on memory related to increased resilience against stress.

Although IF is arguably stressful, both metabolically and psychologically, it produced greater improvements in memory and BDNF for obese adults than weight loss alone. The diet
produced significant changes in potentially mediating factors, including BDNF and leptin, and trends for concurrent improvements in insulin sensitivity and HPA axis function were also apparent. These results are consistent with animal research on calorie restriction and intermittent fasting, which finds specific improvements in learning and memory (Duan, 2003; Duan et al., 2003a; Martin et al., 2006). Although IF is likely to be difficult to translate into regular community practice, it can serve as a useful tool to explore mechanisms that may improve neurocognitive function across the lifespan. Such research may provide the foundation for more widely acceptable interventions to promote cognitive health. In addition, it is worth exploring the frequency and duration of fasting required to produce beneficial effects.

Taken together, the results of this exploratory study suggest that IF involves repeated exposure to mild metabolic stress, with effects that are consistent with the hypothesis that IF can improve memory and increase BDNF in obese adults, and may contributes to more healthy HPA axis function. As the first published test of the effects of IF on human cognitive function, and the first to implement controlled measures of HPA axis function, this exploratory study paves the way for future research into the potential neuroprotective effects of intermittent fasting.
5. Discussion

Losing one’s memory, comprehension and independence are among the most feared risks of growing older (Anderson & McConnell, 2007). However it is not yet clear what differentiates those who experience serious cognitive decline from those who show more healthy cognitive aging. Mounting evidence for “pre-clinical” pathological and functional changes decades before dementia diagnosis has led to a search for factors that can affect neural and cognitive function in midlife or even earlier (Sperling et al., 2011). The lifecourse approach to chronic disease etiology (Kuh & Ben-Shlomo, 2004) suggests that prolonged exposure over many years from even small neurotoxic insults could contribute to cumulative damage that could contribute to more rapid cognitive aging.

5.1 A Lifecourse Approach to Cognitive Aging

A number of important pieces of information are needed to piece together the jigsaw puzzle that is Alzheimer’s disease (AD). Key among these is evidence of factors that can damage human neurocognitive health – at any age. It is now considered likely that AD is a lifespan disease, not simply a disease of old age (Gustafson, 2008). Factors that can protect human neurocognitive health are also particularly needed. Whether or not they directly affect AD etiology, factors that contribute to increased cognitive reserve (Stern, 2002, 2009) may go a long way to buffering the brain against the ravages of AD. Some autopsy studies (Roe et al., 2007) indicate that some people can have AD pathology without ever showing symptoms during their lifetime. For this reason alone it is worth exploring factors that promote good cognitive health.

The existing evidence from epidemiological studies discussed in Study 1 indicates that weight loss, particularly among older adults, is associated with increased risk of cognitive decline and dementia. Obesity is well known to increase risk of cardiovascular disease, diabetes and cancer, some of the leading causes of death in the nation. The risk that weight loss interventions
to protect against these diseases might inadvertently increase risk of dementia is troubling. It is possible that the weight loss observed in these observational studies does not play a direct causal role in the onset of cognitive decline and dementia, but this remains to be established. In either case, weight loss interventions in midlife could be a valuable approach to avoiding potential neurocognitive harm later in life, while concurrently reducing risk of other chronic diseases and improving quality of life.

Consistent with a lifecourse approach to cognitive aging, Study 1 demonstrated empirical evidence from longitudinal studies linking obesity in midlife to greater risk of cognitive decline or dementia later in life. Significantly, the majority of studies that did not produce evidence for such an association were among older adults, a time in life when BMI is a particularly poor indicator of body composition, and when early stages of undetected dementia may already be wreaking havoc on energy balance. While relatively few (e.g. Cournot et al. (2006a) of these longitudinal studies reported cognitive function at midlife when baseline measures of weight were taken, Study 2, the NHANES-III study, produced evidence that increased weight in midlife is associated with worse cognitive function in at least two functional areas: working memory and reaction time. Animal research and the evidence from human PA and CR/weight loss interventions (Study 3) indicates that interventions that affect weight or adiposity in midlife can have neuroprotective effects that correspond to functional improvements in domains such as memory. Consistent with this, study 4 (the DRIFT study) produced evidence of beneficial effects on both weight and memory function in young and middle-aged obese adults.

Taken together, the evidence from these studies is consistent with what would be predicted by a cumulative model within a lifecourse approach to cognitive aging. A cumulative model would predict that the cumulative effects of even small exposures over time can
contribute to increased disease risk, and that removal of the exposure does not reverse the
harm already done. Study 2 reported small but significant differences between the cognitive
function of obese versus non-obese persons in early and mid-adulthood. Study 1 found existing
epidemiological evidence for a link between increased weight in midlife and increased risk of
cognitive decline and dementia later in life. It is possible that exposure to obesity has cumulative
effects on the brain over many years. If true, one would expect neural damage and cognitive
function to worsen with increased duration of obesity. The effects of duration of obesity have
not been widely investigated, and attempts to incorporate this into Study 2 were hampered by
loss of sample size and power. This remains an area in need of further investigation.

5.2 Central Obesity May be More Strongly Linked to Neurocognitive Health than Global
Obesity.

Plausible mechanisms make central obesity a likely culprit in any causal association
between obesity and neurocognitive damage. Central obesity provides a number of potential
mechanisms that could affect cognitive function in the short term or over many years. These
include effects on glucose regulation and insulin resistance, inflammation, HPA axis regulation,
leptin and BDNF. Thus central obesity, rather than global obesity, may be the real concern for
cognitive aging. However to date most research into the association between obesity and
cognitive function has relied on BMI as the sole marker of adiposity. Study 1 demonstrated that
the majority of research to date has relied on BMI as the sole measure of adiposity. This may
have contributed to the mixture of findings in this area, and should be addressed in future
research by the additional assessment of body composition and/or distribution.

Study 2, the NHANES-III study, demonstrated that a measure as simple as WHR is
sometimes more likely to show significant association with cognitive measures than BMI, and
that the strength of the association can be greater. Categories of obesity measured by BMI were
not closely associated with percent fat mass or central obesity measured. In addition, the magnitude of the association of each measure of adiposity with cognitive function differed. Consistent with prior research where central obesity was assessed, the magnitude of the relationship between WHR and attention/memory score was much greater than that found with BMI or percent fat mass. This is not consistent with a spurious finding.

Similarly, the DRIFT study demonstrated that central obesity may be more closely linked to a number of mechanisms that potentially mediate effects of obesity on the brain, including leptin, BDNF and HPA axis function.

Consistent with the hypothesis that obesity affects cognitive function, the NHANES-III study showed a small but significant relationship between increased global or central obesity and worse performance on a test of attention/memory. Though several other cross-sectional studies have found no association, or even the reverse, they have typically been among older adults, who may already be experiencing the weight loss common in dementia. Dementia is typically diagnosed in persons aged >65 years. In the NHANES-III study, increasing weight and worse cognitive performance were related in adults aged 20-59 years. The small magnitude of the association would be expected if this were in fact related to cognitive decline over many years. However causal inferences are beyond the scope of this cross-sectional study. While it is possible that these

5.3 Behavior May Moderate the Association Between Obesity and Cognition

It is possible that the association between obesity and cognitive function is merely an artifact of some other unmeasured factor. Most studies of obesity have controlled for education, age, socio-economic status, ethnicity, or gender, and many for diabetes or cardiovascular risk factors. Fewer have assessed the effect of health-related behaviors known to affect obesity as either potential confounding factors or potential moderators of the association.
However growing evidence indicates that physical activity and quality of diet could affect neurocognitive health. For this reason, study 2 investigated the potential moderating effects of quality of diet, physical activity, smoking status and social support on the association between obesity and adult cognitive function. Quality of diet, social support and smoking status showed independent associations with cognitive function in at least one test. However, only physical activity showed evidence of an interaction between central obesity and cognitive function. Persons who were obese but active showed better cognitive performance that those who were obese and sedentary. This could be a composition effect, and much more research is needed to determine the effects of PA interventions on cognitive function. However some other intervention studies do find support for a causal role for PA on cognition.

5.4 Interventions that Affect Obesity May Reduce Risk of Cognitive Decline

It is difficult to experimentally test the effects of increasing weight on humans. However the effects of weight loss may shed some light on the effects of obesity on cognitive function. Interventions that can affect obesity, either by reducing it, or by mediating changes in mechanisms that affect the brain, have potential utility in this regards. Evidence from animal studies demonstrates that calorie restriction leads to significant neuroprotective effects including preserved memory function with advancing aging, increased synaptic plasticity and neural health, and protection against excitotoxic insults or neurodegenerative disease. In humans the evidence is more mixed. Study 3 showed that, based on the current empirical literature, dieting for weight loss can produce worse cognitive performance. However more of the larger, well-designed studies appeared to support beneficial effects. It is important to understand the effects of weight loss on human cognition, not only because it may inform safety practices around weight loss interventions but also because it may provide insight into the
direction of causation in the apparent relationship between obesity and cognition suggested in epidemiological studies.

In the DRIFT study, 8 weeks of calorie restricted dieting produced significant weight loss (approx. 6%) but did not produce changes in any cognitive domain at 8 weeks. Effects on memory were not apparent until 6 months later, and corresponded to decreased central adiposity and increased BDNF. This finding is consistent with a direct causal relationship between obesity and cognitive function in midlife for health adults.

5.5 IF Produces Beneficial Effects on Memory in Obese Adults

Much more research is needed before solid conclusions can be drawn from the IF study regarding neuroprotective effects. At present the results do suggest that IF is well-tolerated and safe for obese adults in midlife. However the effects on older adults, or adults with existing neurocognitive vulnerabilities remains to be tested. Animal models indicate that IF can have neuroprotective effects against neurodegenerative disease, neurotoxic insult or age-related cognitive declines. However these effects have yet to be tested in humans. At least one study of caloric restriction in older adults with MCI supports a beneficial effect (Krikorian et al., 2012), but the neuroendocrine effects of IF may be distinct and are as yet unknown. Furthermore it is not possible to extrapolate from the results of this 8 week intervention to the longer-term effects that might occur with a public health intervention.

With those caveats in mind, the IF dietary regimen used in study 4 holds good promise for older adults and clinical populations, such as persons with Type 2 diabetes mellitus. IF proved to be safe, well-tolerated and required only a relatively brief intervention (8 weeks) to produce longer term cognitive changes. This warrants further investigation, particularly among persons at high risk for cognitive decline and dementia. Whether or not it eventually proves an acceptable public health intervention, this interesting paradigm of repeated mild metabolic
stress, with some effects distinct from those seen in CR (such as increased neurogenesis, IGF-1, and potentially greater increases in BDNF), should provide an interesting and useful opportunity for better understanding the mechanisms that link human obesity to neurocognitive health outcomes.

5.6 Plausible Mediating Mechanisms Exist

As previously discussed, numerous plausible mechanisms could mediate an effect of obesity on human neurocognitive health. While study 2 did not find evidence that IGF-1, glucose regulation, or inflammation affected the association between central obesity and SDLT or SRTT, there have been many other studies that find evidence of mediating roles. In Study 4, the DRIFT study intervention the direction for change in insulin sensitivity, glucose insulin, BDNF and HPA axis activity were all consistent with the hypothesis of their beneficial effects on neurocognitive health. IF produced significant improvements in memory at 6 months follow-up that were not apparent for the SDR control group. These changes were mediated by greater loss of trunk fat for the IF group that occurred after the end of the 8 week intervention. By contrast memory changes were not associated with change in global obesity (BMI, % fat mass). This finding is consistent with existing evidence that central obesity is particularly important for cognitive function. The reasons for the additional weight loss in the IF group are not known. It is possible that the IF group were more likely than the SDR group to continue some form of dietary restriction after the end of the intervention, though this was not measured. Follow-up studies should investigate this possibility, as well as the possibility that the IF intervention had differential effects on neuroendocrine factors that influenced fat distribution.

Much more work needs to be done to test the tenets of the theory of hormesis (the idea that repeated exposure to mild stress can have cumulative health benefits). In particular the idea that repeated stress/stimulation leads to increased resilience against future stressors of the
same or different type will require extensive testing. As noted previously, an extensive body of literature already documents many detrimental effects of repeated stress, and it would be insufficient to simply state that all of these stressors were above the threshold for detrimental effects. Clearly the hypothesis needs more specification. However it is an interesting theory, and if adopted widely could result in a paradigm shift in many fields involving adaptive systems, including immunology, neuroscience and stress research.

The results of the DRIFT study are consistent with the hypothesis that repeated mild metabolic stress can lead to greater improvements in memory function than weight loss alone. However this exploratory study, with its small sample size and missing data, can at best provide preliminary results to stimulate future research. In this study it was not possible to analyze data on pro-inflammatory cytokines, psychological stress or mood. Furthermore, results of the subset of data available on HPA axis function should be interpreted with caution given the small sample size. However the HPA axis measures showed trends for increased variability of the diurnal HPA axis rhythm, and increased capacity for response to a novel stressor in the IF group that are consistent with expectations that IF would lead to improved HPA axis function and resilience against stress. Since GCs produced by the HPA axis, and GCs produced by central adipocytes, are known to have significant effects on the hippocampal neurons, learning and memory, the ability to improve HPA axis function and reduce central obesity after just 8 weeks of intervention would be valuable.

This was the first test of the effects of IF on human cognition and the finding of a memory-specific effect is consistent with research in animals (Maalouf et al., 2009). Importantly, IF did not lead to the cognitive deficits sometimes found in Ramadan fasting (Roky et al., 2003; Roky et al., 2004; Roky et al., 2000). Indeed IF did not have detrimental effects on cognitive performance though it was metabolically stressful throughout the study, as indicated by
decreased serum glucose. Unfortunately enough data were missing from psychological questionnaires that it was not possible to determine whether the diet was also psychologically stressful, but it is reasonable to assume that fasting involved some stress for most participants.

The DRIFT study has demonstrated the capacity of IF to improve memory and increase circulating BDNF in obese adults after 8 weeks of intervention – and a delay of 6 months. The magnitude of the change in memory by 6 months was small, but important.

5.7 Strengths and Limitations

Though suggestive of an association between obesity and cognitive function that can be affected by repeated exposure to mild metabolic stressors, the studies reported here had several limitations that prevent definitive conclusions.

5.7.1 Strengths and Limitations of Studies 1 and 3: Systematic Reviews

The systematic literature reviews conducted on the association between obesity and cognitive decline and dementia (Study 1) and the effects of weight loss interventions on adult neurocognitive health (Study 3) provided an excellent overview of the existing empirical literature in these areas. However they were limited to the MEDLINE and PsychINFO databases, and as such do not contain all of the available literature on these topics. Furthermore, the value of these reviews is limited to the quality of the studies that are available. Most of these studies controlled for potential confounding factors such as education, ethnicity, age, and gender, and many controlled for vascular and metabolic factors, other potential confounding factors such as obstructive sleep apnea were not addressed. This study aimed to encompass all of the available literature, and so deliberately did not select for the studies with the best quality designs and execution, which naturally have a significant effect on the validity of their results. A next step in this review process will be to review other databases (Cinahl, Embase, Google Scholar) and
apply quality ratings to all the available studies. This will give a better estimation of the strength of the available evidence, where the current review focuses principally on the quantity.

5.7.2 Strengths and Limitations of Study 2: The NHANES-III Study

The cross-sectional design of the NHANES-III study prohibited causal inferences or extensive statistical modeling of the association between obesity and cognitive function. While the NHANES-III study is the only NHANES study to date to include cognitive outcome measures, the measures used were limited. The SDLT, for example, ranged from 0 – 16, and had obvious floor and ceiling effects that may have contributed to the small amount of variance explained by regression models. Similar low estimations of variance explained have been reported by other researchers using the same dataset for other studies (Pavlik et al., 2004; Suhr et al., 2004). A more full neuropsychological test battery would provide significantly more information. Though useful in this exploratory study, many other variables available in the NHANES-III study were far from the ideal. For example bioelectric impedance analysis (BIA) is not the gold standard in measurement of body composition, though our calculated values for fat mass were correlated with WHR and BMI. In addition self-report is not the most reliable measure of physical activity, and follow-up studies would benefit from objective measurement by actigraphs. Furthermore, some potentially relevant mediating, moderating or confounding factors were not measured as part of the NHANES-III study. While it would have been good to test stress and HPA axis-related hypotheses in the general population, the NHANES-III study was not designed to assess psychological or physiological stress. No measures of perceived stress or glucocorticoid secretion were available. Similarly, measures of some potential confounding factors, such as obstructive sleep apnea, were not included.

Given the age of the NHANES-III dataset, with data collected between 1988-94, it is also possible that societal factors may have changed, and that results would be different if collected
today. For example familiarity and comfort with computer use would not have been as widespread in 1988-94 as it is today. Lack of familiarity with computers could have caused some people to perform more poorly, confounding the results. Rates of obesity in the population are now higher than they were in 1988-1994. If the association between weight and cognitive function reported here was an epiphenomenon of other differences in the population that were also related to obesity, then more widespread obesity would tend to attenuate the strength of the association. Comparison of our results with data collected more recently would provide useful insights into these possibilities. The most recent NHANES study has apparently included some cognitive measures, so further exploration of this question may soon become a possibility.

In spite of these limitations the availability of behavioral and anthropometric and cognitive measures together in a large nationally representative sample made it possible to assess the hypotheses. While other studies have shown an association between adiposity and cognitive decline or dementia, to our knowledge no other studies have concurrently assessed the potential for behavioral factors to moderate this association. The sample size of the NHANES-III study was a real strength, allowing the power to control for multiple covariates or confounding factors and making regression model-building possible.

5.7.3 Strengths and Limitations of Study 4: The DRIFT Study

This exploratory R21 study was originally powered to detect between-group differences in weight loss. While the sample size is appropriate for this purpose it did not provide the power needed for statistical tests of change in many of the secondary outcome variables, such as insulin sensitivity. The small sample size also prohibited regression model-building or structural equation modeling that could have provided an understanding of the causal relationships between observed changes. A further loss of data through internal study errors
such as incomplete tests, missing samples, study attrition at the 6 month follow-up, and the inability to retrieve some data further compounded these issues.

The potential to explain the differences seen at 6 month follow-up was limited by the absence of any measures of participant behavior in the intervening 6 month period. It is therefore impossible to determine whether some participants continued the IF dietary regimen beyond the study period, whether some participants engaged in more physical activity and so forth. In addition to these variables, future investigations of IF should include measures of physical activity, sleep patterns, self-image and self-confidence, self-efficacy for behavior change, and systematic collection of feedback on the lived experience of being on the study diet. Qualitative information on factors that influenced adherence to the study diet would strengthen future research and practical application.

Furthermore, the potential to translate the results of this study into community practice is limited. For safety reasons this R21 pilot study employed highly restrictive exclusion criteria that may have led to a sample that was not representative of the general population. In addition, much of the recruiting was done on an academic university campus, making it likely that the sample was more educated than the general population. The invasive and intensive nature of the study also made selection bias likely.

In addition, IF has limited face validity or ecological validity as a sustainable intervention for prevention of cognitive decline. In the general population adherence to alternate day fasting principles may be difficult. Eating is a highly social practice and carries many cultural and emotional meanings.

Rather than using this study to promote widespread adoption of IF for cognitive health this study can be used as an unique opportunity to investigate the distinctive mechanisms that may underpin the effects of IF. The idea that repeated exposure to stress can have cumulative
beneficial effects is not widely accepted, and has not been widely tested. The DRIFT study provides evidence that should encourage further investigation, as IF may provide clues to mechanisms that promote neurocognitive health. A better understanding of these mechanisms may help to lay the foundation for future interventions to promote neurocognitive health.

In spite of its limitations, the DRIFT study successfully implemented a rigorously controlled intervention protocol that employed optimal measures of the outcome variables of interest. The use of DXA scans for body composition, FSIVGTT for insulin sensitivity, and the 90% V02max stress test are good examples of this. Furthermore a large number of useful variables were measured, making this a rich source of information on the effects of IF on the health of obese adults.

5.8 Novel Contributions

To date this is the first published study of IF to include a thorough investigation of effects of IF on HPA axis function in humans. As previously described, one other study of IF in humans measured cortisol at a single time of day, but did not control for different time of day for the two study groups, thus confounding the results (Stote et al., 2007). Given the trends for improved HPA axis observed in this study, the DRIFT study can provide important preliminary data to inform the development of larger study of these effects.

This is also the first study to assess the effects of IF on human cognitive performance. The cognitive test battery used was designed for repeated measures, had good reliability and validity, and was practical for implementation in the study visits. Hence this exploratory study is uniquely placed to investigate the theoretical effects of this weight loss diet on human cognition and potential hormetic mechanisms. Given the evidence of significant neuroprotective effects of IF from animal research, investigation of the effects of IF on human cognitive function may be important to our understanding of cognitive aging.
Furthermore, Study 2, using the NHANES-III data, provides a novel assessment of the association between obesity and cognitive function in the general population. Unlike prior studies showing an association between obesity and cognitive decline or dementia late in life, the NHANES study provided evidence of an association in early and mid-adulthood, and assessed potential for health behaviors to moderate the association.

5.9 Future Directions

In spite of the wealth of information on the systemic effects of obesity on health, relatively little is known about the effects of obesity on brain health or cognitive function. The present exploratory study provides further evidence of a link between obesity and cognitive function, and highlights the particular importance of including measures of central obesity in future studies. Future epidemiological research in this area should also include repeated measures analysis with rigorous assessment of cognitive function baseline. Weight loss intervention studies with larger and more diverse samples will also be an important source of information.

Assessment of the impact of repeated mild stress on the association between obesity and cognitive function was a particularly novel contribution of the present study. The idea that repeated stress can be beneficial rather than detrimental requires much more investigation. Directly comparing the effects of different stressors would be a useful start to a better understanding whether a common mechanism does indeed underpin effects of repeated stress on health. Intervention over a longer duration may help to clarify whether it was the intervention or post-intervention behaviors that contributed to 6-month between group differences in the DRIFT study. The potential for IF to improve cognitive function in persons with diabetes and/or MCI would also be a logical next step. These studies should be sure to include measures of physical activity, sleep, social interactions at meals, and psychological stress.
to assess the impact of the intervention on these factors, and their potential role in outcomes. Finally, future studies should investigate the frequency and duration of fasting required for an effect, or alternative “stressors” with similar effects, since alternate day fasting is unlikely to become a widespread public health practice.

5.10 Summary

In conclusion, the findings from the present study provide evidence that increased weight is related to poorer performance on an attention/learning task in a large, nationally representative sample of adults aged 20-59 years. Consistent with prior research, the finding was particularly strong for central obesity, highlighting the importance of including measures of central obesity in future research. As predicted, the association between central obesity and attention/memory scores was moderated by frequency of physical activity, but not other health-related behaviors. Regular physical activity and intermittent fasting can both be considered examples of repeated stress, or hormesis, and emerging evidence suggests that repeated mild stress can have beneficial effects on allostatic load and cognitive aging. Consistent with this hypothesis, intermittent fasting produced significant improvements in memory, BDNF and trunk fat of obese adults, as well as trends for improvement in HPA axis function. These findings provide an important extension of the existing literature on hormesis and the effects of stress on cognitive health. Further comprehensive testing of these effects in early and mid-adulthood may provide important insights into the cognitive deficits that can predate the development of dementia.
APPENDIX

This report serves as an opportunity to reflect on the clinical observations made and the experience that I gained through my involvement in the Colorado Clinical and Translational Science Institute (CCTSI) Pre-doctoral training program at the University of Colorado Denver. This training program provided the opportunity for students from non-clinical doctoral training programs to gain skills and insights that would equip them to better translate research in their field into real-world practice. Didactic learning, seminars and discussions provided only part of the learning experience – the most valuable aspect was the opportunity for direct exposure to the realities of patient experiences, patient care and clinical practice. Clinical placements were individually tailored to reflect each student’s area of research. With my interests in promoting healthy cognitive aging, preventing cognitive decline and Alzheimer’s disease, clinical observations of memory clinics and neuropsychological testing services were a logical choice of placement to complement my concurrent didactic learning and the research accomplished and described above. Furthermore, since my work focused on the potential that overweight and obesity may play a causal role in increasing risk of age-related cognitive decline or dementia, exposure to weight management services was also a logical choice. As a result I completed three distinct clinical placements through the CCTSI training program, in addition to extra-curricular volunteer work with the Alzheimer’s Association Helpline and involvement in relevant clinical trials at the University of Colorado Denver. Placements were at: 1) the Weight Management Clinic at Kaiser Permanente Colorado, 2) the Clinical Neuropsychology unit at National Jewish Health Colorado, and 3) the newly established Memory Clinic at Kaiser Permanente Colorado. These placements were supervised and/or arranged by my clinical mentor, Dr. William Donahoo, M.D.
Since I learned much that was practical, useful and interesting from these experiences the focus of this report gives an overview of just some of what I learned, and a reflection of how this has shaped my understanding of the field, and current and future research.

**Clinical Placement 1: Kaiser Permanente Weight Management Clinic**

Supervised by endocrinologist Dr. William Donahoo, M.D., my placement at the Kaiser Permanente weight management involved accompanying Dr. Donahoo in the weight management clinic to a) group visits and b) individual patient consultations for weight management. All patients were insured by Kaiser Permanente Colorado

*Weight management groups*

At the time of my clinical placement, the group visits were a very new addition to the weight management services offered locally by KP Colorado. As explained by Dr. Donahoo, the benefit of group visits for patients was that they involved a lower copay and shorter waiting period than individual visits. In addition, the rationale for group visits may have been drawn from research such as that describing how behavior modification group visits and medication use together were the most effective treatment for weight loss.

The weight management group visits at this clinic in KP Colorado were made up of patients seeking information and options for weight loss, particularly those seeking medications to assist weight loss. Group participants did not know one another, and the need for confidentiality was described before the start of the group. They were not intended as therapeutic groups or support groups. At the time of my placement the groups were offered as a single session, chiefly providing information about different weight management options.
There was an expectation among staff and providers that they would introduce group follow-up visits in the future.

The group sessions were run by a nurse and the endocrinologist, Dr. Donahoo. As part of the visit, all patients received confidential weight and blood pressure check conducted individually, that was included in their medical records, and through this and other individual conversations the nurse did a lot to quickly build rapport with the patients. The remainder of the group session was chiefly comprised of information about different weight loss options, and the opportunity to ask questions and discuss the options together as a group. Patients were also offered the opportunity to ask the doctor questions specific to their own medical needs, at the end of the group in a confidential setting. Surprisingly, only a few patients tended to take up this offer.

I learned much from these groups. First, I found it informative to listen and learn about the different weight management options that are available. Prior to this I was not familiar with any of the medications that can be used in weight loss efforts. I became aware of a number of weight loss drugs, including Orlistat (Xenical), which reduces fat absorption by acting on an enzyme responsible for cleaving fat. Though it can be effective in producing 5-7% weight loss in 3-6 months for some people, there are medical contraindications and side-effects that may limit its widespread use. By contrast, Sibutramine (Meridia), has serotonergic action and was originally developed to treat depression, but was found to act on brain regions responsible for hunger/satiety. It can have additive, or interactive effects with a number of other drugs, such as SSRIs, pseudoephedrine, or the over-the-counter herb St John’s Wort. This was the drug which had interested most patients enough to attend the group session, even though the cost of the drug was not covered as part of patients’ insurance. The apparent widespread interest in this
drug was itself interesting. Where were patients learning of this option? What was driving the demand for this medication? Clearly many patients in the groups found medications more appealing than behavior change options for weight loss.

Behavior change options for weight loss were also discussed in the group visit. The options discussed were those available and insured through KP Colorado. These included 1) a free online program to develop individually tailored weight loss strategies, 2) a phone support program that provided 1:1 customized weight loss programs, 3) a free CD to help people identify unhealthful foods in their kitchens, 4) dietician visits for persons with additional medical issues beyond overweight or obesity, such as diabetes, 5) discounts at Weight Watchers, and 6) Optifast, a medically-supervised fasting program for persons with BMI >30.

The value of group dynamics in this setting became apparent in a number of ways. As already described, these were not therapeutic groups. However patients were able to share and discuss some of their own experiences with different weight loss options. For example during the discussion of Orlistat, the group was asked if anyone had personal experience using this drug. A few patients raised their hands, and reported significant issues with oily stools. Even more interesting was the discussion between two patients who described their observations of the extreme and enduring physical and psychiatric/behavioral effects of the drug Phentermine on friends who had used it. This drug is not supported by the KP physicians or clinic, and so was not included in the information provided to all patients.

*Individual weight loss consultations*
After the morning group visits I attended, I was able to observe individual patient appointments in the weight management clinic. These provided useful insights into the running of clinical weight loss practices, as well as the kinds of issues faced by patients who are obese.

From a practice standpoint, each patient was weighed by a nurse before seeing the doctor. The physician had access to the full medical record for each patient, allowing him to quickly access any relevant medical history that may be affecting weight. The consultations were typically fairly structured, and the types of questions and information that patients sought tended to be similar. For example patients were likely to be aware of the benefits of weight loss by physical activity and dietary restriction, and instead wanted information about medications or bariatric surgery. This was accommodated, with information on the latter readily displayed using pre-prepared information boards. Each patient left with a letter outlining the things discussed and their various options. They were also usually also told they could contact the physician with questions and for the results of any tests that were ordered. These provided fairly systematic approaches to addressing weight management in patients. I also learned that candidates for bariatric surgery were encouraged to try other options first, and were carefully vetted and counseled before surgery was indicated.

Some of the issues faced by patients, and their barriers to weight loss, can be illustrated by some of the following cases.

*Patient case study #1* was a man in his 50’s who appeared surprisingly average in weight, likely reflecting my own personal expectations and norms for weight of a man his age. This itself was an interesting surprise, as were the various other patients who attended the clinic who did not appear overweight to my eye. Patient 1 reported struggling with his weight for 15-20 years
without much success in weight loss. He was clearly concerned about his current weight. As a smoker, he reported being ready to quit, but was concerned about the potential for weight gain if he did so. Interestingly, while he arrived at the clinic officially asking for a prescription for the drug Meridia, further discussion revealed that he was really interested in bariatric surgery. Both he and his wife had applied. His wife had been accepted, but he had been denied. Altogether this patient provided interesting insights into the variety of motivations that can drive motivation for choosing or avoiding different weight loss options.

*Patient case study #2 was an older woman, perhaps mid 60’s, with a BMI of 36. She had multiple significant health concerns, including cardiovascular problems, Type 2 diabetes mellitus, thyroid problems and back problems, and used oxygen supplied by a nasal tube. Despite this she was still working as a nurse. She reported being quite thin until after having her third child, when she gained quite a lot of weight, then later gained further weight when she injured her back. The back problems continue to make it difficult to walk or exercise, and as she has gained weight physical exertion has become increasingly difficult. With adult children and grandchildren now living with her she continues to find many barriers to self-care. Again, this patient provided many insights into the barriers to a healthy weight that some people face.*

Clinical Placement 2: National Jewish Health Adult Neuropsychology Clinical Service

The Adult Neuropsychology Clinical Service at National Jewish Health provides neuropsychological evaluation for many different conditions. The results of the neuropsychological tests are used to complement information from medical history, laboratory work and imaging such as MRI or CT scans. My placement at the clinical neuropsychology unit, which was overseen by Dr. E. Kozora, a highly experienced a clinical neuropsychologist, provided
very useful insights into the nature of truly comprehensive neuropsychological assessment for potential dementia. I attended a number of all-day testing sessions designed to assess patients who had been referred to the clinic for potential Alzheimer’s disease. It was useful to learn about the flow of events in conducting these testing sessions, the personnel and training required, the nature of the tests themselves, and the way that [this sample of] patients responded to taking the test battery.

Patients were usually referred by another healthcare provider. The neuropsychological testing was usually covered by insurance, though some patients could choose to pay out-of-pocket if they chose to do so. The testing was collaboration between the clinical neuropsychologist responsible, and a specially trained technician, usually with a bachelors in psychology or more. The file of tests and scoring sheets was compiled by the technician in advance at the beginning of the day. Patients were scheduled for a very long day of testing, often 9am – 4pm, with a 45 minute break. During this time they saw the clinical neuropsychologist, who would take a history, and completed a variety of paper-and-pencil neuropsychological tests administered by the technician. The results of the tests were reviewed by the clinical neuropsychologist, who also prepared an in-depth report. Patients were encouraged to bring a friend or family member, at their discretion. These were particularly helpful in the assessment of dementia, as the patient themselves may not be able to recall much of their own history, or may not have much insight into the changes that had occurred in their daily function.

The neuropsychological test battery used during the assessment of dementia included a range of widely accepted tests. Tests included Trails A and B, the Dementia Rating Scale II, the Brief Visuo-spatial test-revised, a test of logical memory, the Boston naming test, and the
Wechsler Abbreviated Scale of Intelligence. As a result, across the visit patients could expect to do writing, drawing and answer some questions verbally. Interestingly, the day also included a test of effort, to gauge the extent to which patients were trying their best. I was interested to note that the word “test” was used liberally when talking to patients, which may be the reason some persons with dementia asked questions like “Do you have other students who come in as well?” Overall, I found that the testing day, though long, was conducted in a gentle, low-stress manner. Technicians were attentive to how tired a person was becoming as the day progressed, and responded accordingly.

Patient case study #3 provides a snapshot of the testing experiences I observed. An 86 year old Caucasian woman attended the clinic to be assessed for potential Alzheimer’s disease. Her husband and medical provider had raised concerns about her memory and function, and she was happy to go along with the assessments by the doctor/s and neuropsychologist. She was articulate, well-dressed, had good comprehension of requests and directions. Her hearing and eyesight were good. Her education comprised of high school education followed by a few short courses over the years. She had been married for 67 years and had two children in their 60’s, both in good health. Her mother had AD for about 10yrs before death. Both the patient and her husband were lean and physically active on a regular basis for many years. The patient had been in a serious car accident 50 years ago, after which she lost consciousness for 10days. She had amnesia for the event but reports returning to full function with no personality change or other notable changes. This patient was unclear on the reasons for attending the testing session, but was very happy to go through with the testing, and appeared to try her best at the tests. She got lost trying to return from the bathroom at a bathroom break. During the testing she struggled with Trails B, and many of the tasks on the Dementia Rating Scale, including differences,
similarities and verbal recall. In the Wechsler Abbreviated Scale of Intelligence she had some
difficulty with block design, and some others.

Overall, the patient showed a trend for reduced function in her activities of daily living,
and her performance on many of the cognitive tests was below what would be expected for
someone of her education and age. Her pattern of performance was consistent with
Alzheimer’s disease. Given my research into the possible effects of obesity and lifestyle factors
on the risk of dementia it was worth noting that this patient had been physically active for most
of her life, and had never been overweight or obese, nor did she have significant health
concerns beyond a history of a traumatic brain injury 50 years ago. As I continue research into
the effects of obesity and lifestyle factors on healthy cognitive aging it is worth remembering
that these factors are neither necessary, nor likely to be sufficient, to cause Alzheimer’s disease.

In summary, my clinical observations during this placement provided many insights into
the practice of thorough clinical neuropsychological testing for Alzheimer’s disease. It is worth
noting that these assessments form part of the diagnostic process for patients who receive
them. Furthermore, many patients never receive such formal and rigorous testing, and their
clinical diagnosis rests on their history and clinical judgment.

Clinical Placement #3: Kaiser Permanente Memory Clinic

The Memory Clinic at Kaiser Permanente (KP) Colorado was newly established only
weeks before I began my clinical placement there. The team working in this clinic included
specially trained nurses, general practitioners with special interest and training in geriatrics,
social workers, administrators, and geriatric psychiatrists. The clinic rotated around different KP
sites in order to maximize accessibility for patients – hence it did not have its own dedicated clinic space, but rather used available free space within various clinic locations.

The clinic provided a particularly interesting opportunity to learn due to the manner in which it was integrated into the overall care provided through the HMO. Patients were referred from internal KP physicians, and the referral and medical records were accessible to the Memory Clinic team in advance of the appointments they had within the clinic. The Memory Clinic team truly worked as a team – meeting together at the beginning of the day to discuss the cases for the day. This ensured that the wisdom of more experienced and highly trained members of the team was shared efficiently, while ensuring that the clinical judgments and actions of those more new to the field were appropriately supervised.

The clinic was structured to provide a sequence of at least two visits for all patients who were referred – an initial assessment and then a follow-up for discussion of results and diagnoses. Ongoing care could also be provided to those how needed it. The initial assessment visit included collecting medical history, a physical examination that covered relevant neurological aspects, and a sequence of neuropsychological tests. The latter included the Dementia Rating Scale II and Trails B, among other possible tests. With patient permission, an accompanying family member or friend could provide additional information during the medical history and also in a separate interview with a social worker. Where history or medical examination suggested a need for additional medical tests (such as an MRI or blood tests) these were also ordered through the KP system and results were available to the team before the next Memory Clinic visit. Another advantage of the integrated health records was the ability to view patient medications that had the potential to affect memory or cognitive performance, and suggest changes before further testing was completed. The presence of prescribing physicians
ensured that those patients who needed medication changes, or perhaps had medical conditions which required the introduction of new medications to help stabilize the health of a patient, could be treated immediately, with direct communication with the regular primary care physician. I was impressed by the efficiency and integration of these services. The diagnostic process appeared to provide a thorough, whole health, perspective. Diagnosis was made by the team at the team meeting.

Patient follow-up visits were made once all of the relevant tests were assessed and the medical history reviewed as a whole. Where necessary, diagnoses were given to a patient in a sensitive manner by the person who had seen them, and who had coordinated their overall assessment. At the same visit, a consultation with a social worker was also included for those patients who were given a diagnosis of dementia. During this visit they were offered resources for understanding and coping with dementia, and referrals to other services. The time spent with the social workers seemed a highly valuable component of the services provided. It was pleasing to see that patients were not simply left with a diagnosis and uncertainty about what to do next. They were left with practical help, ongoing contacts, and the expectation of continued holistic care.

During my placement I was able to observe many different consultations, both assessment, giving of diagnoses, and also follow-up visits for those who had previously received a diagnosis of Alzheimer’s disease and needed behavioral or medication review. It was interesting to note the seemingly large proportion of patients attending the clinic who had diabetes. This was consistent with what my literature review had shown regarding the increased risk of cognitive impairment with Type 2 diabetes mellitus can. I therefore asked a physician at the clinic about their subjective impression of the proportion of patients referred for memory
problems who had diabetes. He thought that most patients had diabetes, certainly more than 50%. Anecdotally I also noted that a lot of patients were overweight, though this should come as no surprise given the high rates of overweight and obesity in the general population. Similarly, relatively few patients were physically active on a regular basis, but this too is quite common in the general population, and particularly among older adults.

I found it very interesting to see how many different patients with subjective memory complaints presented for clinical assessment. This varied widely. Some clearly presented with very limited function and comprehension of their surrounds, while others appeared quite functional, but testing revealed significant deficits. Many patients had very little insight into the problems reported by their caregiver, spouse or friend who accompanied them. Since this was an insured population, I expect that the patients attending the clinic were more likely to be at a higher level of function than the general community, consistent with subjective observations I have made in comparison with those people calling the Alzheimer’s Association Helpline, where I also volunteered for more than a year. That being the case, the difficulties faced by persons experiencing significant memory decline and dementia should not be underestimated. People who are unaware of their problems, or even resistant to the idea that they have problems, are likely to be underserved unless represented by a caring and capable family memory or friend. Furthermore their care options are constrained by their resources and the services available in their community. Where they can be supported by an integrated healthcare system, reversible causes of cognitive deficits – such as some medications not appropriate for older adults – can be detected and deal with to maximize healthy function. Where dementia diagnosis is clear and gradual decline is inevitable, comprehensive medical and social support make a significant difference to a person’s quality of life.
In summary, my time at the KP memory clinic provided very interesting and very informative insights into the background and lived experience of a wide variety of people with memory problems. It also provided an opportunity to learn about the full diagnostic process for dementia and similar disorders that has proven invaluable as a scholar and as a professional.

Summary of clinical observations and relevance to research

Clinical placement at the KP weight management clinic provided the opportunity to learn more about the challenges to managing a healthy weight faced by persons who are overweight and obese. It was also a chance to learn about the different treatment options for weight management. With my training in psychology, public health and behavioral science my prior exposure had principally been to behavioral lifestyle change options. It was therefore useful to learn about additional options such as medications, bariatric surgery and specialized fasting or weight management programs. My dissertation research focuses on the effects of overweight and obesity on cognitive function in adults. It was clear that there are many factors related to obesity that could contribute to cognitive issues. Depression, social isolation, pain from past injuries or poor health and functional limitations caused by obesity itself could contribute to the cognitive deficits that have recently reported in persons who are overweight or obese. The extent to which these factors are causally related to risk of dementia should also be investigated.

Placement at the clinical neuropsychology unit at National Jewish Health provided quite a different chance to learn about the intricacies of rigorous cognitive testing. This testing by highly trained professionals may be the gold standard of cognitive testing, and when combined with other sources of information such as medical history, laboratory tests and medical imaging,
can provide a thorough assessment and diagnostic procedure. However many patients do not have access to such services, and many do not have the health or stamina to undergo a full day of testing. This clinical placement therefore provided a valuable opportunity to inform my understanding of what a diagnosis of dementia or Alzheimer’s disease really means, exploring the tests used, functions measured, and providing an excellent opportunity to talk with a number of people with specialized expertise in neuropsychological assessment. My dissertation research builds on an understanding of a need to create opportunities for earlier diagnosis and treatment for cognitive decline. Will this involve more sensitive neuropsychological tests, novel biomarkers or careful imaging techniques? Perhaps all of the above are needed to describe the function and underlying pathology accurately. In any case, a thorough understanding of cognitive and functional assessment is vital to pursing research in this area. Without it research in this field will not be valid or reliable.

Finally, my experience at the KP Memory Clinic provided many valuable insights into the ways that people present with memory problems, as well as the background and history that may accompany cognitive decline. The goal of both my dissertation research and my ongoing research in this field is that my work will have real-world applications to the clinic and community. Thus learning more about the lives of community-dwelling adults experiencing these problems in daily life was invaluable. Furthermore, clinical applications are made difficult without knowledge of what clinical practice really looks like, and who practices it. Of course clinical practice varies from place to place, but it was invaluable to observe an integrated, holistic approach to assessment of cognitive decline that was efficient, professional and caring. My subjective observations of high rates of obesity, diabetes and related issues consistent with the literature I encountered during my dissertation research and the findings of my own studies,
thus making the problems seem more real and less theoretical. A better understanding of the realities of clinical practice shall inform my future research will seek to provide practical, realistic interventions to reduce risk of cognitive decline and dementia, and primary, secondary and tertiary prevention efforts to promote healthy cognitive aging.

Taken together, these clinical observation opportunities have been highly valuable for informing the depth of my dissertation research, as well as laying the groundwork for further translational research in this area.
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