

Aerobic Exercise, Diet, and Neurocognition among Individuals with High Blood

Pressure

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Dissertation submitted in partial fulfillment of the requirements for the degree of
doctorate of Philosophy in the Department of Psychology and Neuroscience in the
Graduate School of Duke University

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ABSTRACT

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Abstract

In addition to the adverse effects of high blood pressure (HBP) on cardiovascular disease, HBP is also associated with increased risk of stroke, dementia, and neurocognitive dysfunction. Although aerobic exercise and dietary modifications have been shown to reduce blood pressure, no studies have examined the effects of a combined aerobic exercise and dietary intervention on neurocognition among individuals with HBP, a group at elevated risk for neurocognitive dysfunction. As part of a larger investigation, the ENCORE study, this study examined the effects of dietary modification alone and combined with aerobic exercise on neurocognitive function among individuals with HBP. One hundred twenty five individuals with high normal blood pressure were randomized to an aerobic exercise and dietary modification group (DASH + WM), dietary modification alone (DASH-A), or a usual care control group. Participants completed a battery of neurocognitive tests assessing executive function and vigilance at baseline and again following the four month intervention. Following the intervention, participants in the DASH + WM and DASH-A groups exhibited modest improvements in neurocognitive function relative to controls, and these changes appeared to be mediated by improved cardiovascular fitness and weight loss. A combined aerobic exercise and dietary intervention improves neurocognitive function among individuals with HBP.

Dedication

To my best friend and love of my life, Angie.

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1. Introduction

1.1 Epidemiology and Health Consequences of High Blood Pressure (HBP)

It is estimated that nearly one in three adults has hypertension (HTN), defined as systolic blood pressure (SBP) greater than or equal to 140 mm Hg or diastolic blood pressure (DBP) greater or equal to 90 mm Hg (Rosamond et al., 2007), corresponding to approximately 50 million Americans and one billion individuals worldwide (Chobanian et al., 2003; Qureshi, Suri, Kirmani, & Divani, 2005). Approximately 95% of individuals with HTN have high blood pressure (HBP) without a definitive cause, referred to as *essential* HTN. An additional 40% of adults have pre-HTN, defined as casual blood pressure (BP) readings of 120-139/80-89 mm Hg (Rosamond et al., 2007). Taken together, the most recent estimates from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure indicate that approximately 106 million Americans suffer from HTN or pre-HTN (Chobanian et al., 2003; Qureshi et al., 2005). Moreover, the prevalence of HTN increases progressively with age, such that 50% of individuals aged 60 years or older have HTN (Burt et al., 1995; Appel et al., 2003) with a lifetime prevalence of 90% (Vasan et al., 2002), underscoring the importance of this ubiquitous cardiovascular risk factor.

HTN is one of the leading causes of disability in the world and is associated with incident coronary heart disease and stroke in a dose-response fashion (Kannel, Vasan, &

Levy, 2003; Dzau et al., 2006; Kannel et al., 1981). Individuals with unmanaged HTN are more likely to develop peripheral artery disease, left ventricular hypertrophy, and heart failure (Chobanian et al., 2003). For individuals over age 40, each 20 mm Hg increase in SBP is associated with a two-fold risk of death from stroke, ischemic heart disease, and death from other vascular causes, and this risk gradient emerges at BP levels as low as 115/75 mm Hg (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002). In addition to the impact of HTN on cardiovascular endpoints, elevations in BP, particularly SBP, are predictive of end-stage renal disease in a dose-response fashion (Klag et al., 1996). Underscoring the impact of HTN on vascular health, the World Health Organization (WHO) estimates that suboptimal BP (>115 mm Hg SBP) is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease (World Health Organization, 2002).

Although it has long been recognized that HTN increases the risk of stroke (Turvey, 1954) and hypertensive encephalopathy (Oppenheimer & Fischberg, 1928), only recently has the relationship between HTN and more common neurological disorders been investigated. Recent studies examining of HTN and brain function have garnered attention as HTN has been associated with an increased incidence of mild cognitive impairment (MCI) (Kilander, Nyman, Boberg, Hansson, & Lithell, 1998), Alzheimer's disease (AD) (Skoog & Gustafson, 2003; Skoog & Gustafson, 2002; Li et al., 2007), vascular dementia (VaD) (Launer et al., 2000), and Parkinson's disease (Scigliano et al.,

2006), raising the possibility that HTN may result in cortical damage above and beyond the ischemic damage observed in white matter degradation (Gianaros, Greer, Ryan, & Jennings, 2006). Moreover, hypertensives exhibit decreased perfusion in a wide range of brain areas relative to normotensives, with perfusion decreasing more rapidly over time in the presence of HTN (Beason-Held, Moghekar, Zonderman, Kraut, & Resnick, 2007).

1.2 Assessment of Blood Pressure

BP is typically measured during outpatient physician visits using automated assessments that follow a standardized protocol (Chobanian et al., 2003). Preceding the assessment, patients are typically asked to avoid consuming caffeinated drinks, exercising, and smoking for a minimum of 30 minutes prior to measurement. Patients are asked to sit quietly for at least five minutes with feet on the floor and arm supported at heart level. An appropriately sized BP cuff (cuff bladder encircling at least 80% of the arm) is used to take several BP measurements (i.e. at least two) to ensure that measurements are accurate.

Manual measurements have become less common as automated BP assessments have gained wider clinical usage. For manual determinations, palpated radial pulse obliteration pressure is used as a starting point to estimate SBP. The cuff is subsequently inflated 20 to 30 mm Hg above this level for the auscultatory determinations, and then deflated at a rate of 2 mm Hg per second for auscultatory readings. SBP is defined as the point at which the first of two or more Korotkoff sounds are heard (onset of phase 1),

and the disappearance of Korotkoff sounds (onset of phase 5) is used to index DBP.

Despite the frequency of office BP assessments and their standardized administration, clinic BP measurements have several limitations. As many as 20 to 35 % of individuals diagnosed with HTN experience 'white-coat' HTN (Pickering, Coats, Mallion, Mancia, & Verdecchia, 1999; Pickering, 1998), in which BP is elevated perhaps in response to the medical setting. Because clinic assessments provide an index of BP in a controlled setting, these assessments may not provide an accurate measure of BP as it occurs during the course of daily life. To address these limitations, ambulatory blood pressure (ABP) assessments have gained wider clinical usage over the past decade, offering several advantages relative to clinic assessments. First, ABP assessments provide a more generalizable index of daily BP and have the additional benefit of providing an estimation of the percentage of BP readings that are abnormally elevated over the course of the day, the overall BP load, as well as the extent of BP fall during sleep. Second, ambulatory measures have been shown to more accurately predict target organ damage in some studies (Verdecchia, 2000; Clement et al., 2003). Despite these advantages, the specificity of ABP is somewhat lower than repeated clinic BP assessments, as ABP is influenced by a variety of exogenous factors, including differences in physical activity, daily caffeine intake, and medication use.

1.3 Impact of HBP on Neurocognitive Function

There are abundant data from both cross-sectional (Birns & Kalra, 2009) and

longitudinal studies demonstrating that HTN is associated with poorer cognitive function and an increased risk of cognitive decline with age (Duron & Hanon, 2008). The vast majority of extant studies have found that HTN adversely impacts cognitive function, although findings may vary depending on the definition of HTN, the duration of follow-up, the type of cognitive task used to assess neurocognition, and the metric used to identify individuals with 'cognitive decline', which is often empirically derived (Duron et al., 2008). In addition, although the majority of observational studies have found an inverse linear relationship between BP levels and cognitive performance, the nature of this association is not consistent across studies, with several noting a 'J-curve' (Okumiya et al., 1997), 'U-shaped' (Glynn et al., 1999; Bohannon, Fillenbaum, Pieper, Hanlon, & Blazer, 2002), or quadratic relationship (Hebert et al., 2004). The magnitude of this effect is therefore difficult to characterize, but based on the available data, HTN appears to roughly double the risk of cognitive decline over time (Duron et al., 2008). Tzourio and colleagues (Tzourio, Dufouil, Ducimetiere, & Alperovitch, 1999) reported that HTN (defined as SBP > 160/95 mm Hg) was associated with an approximate 3-fold increase in risk of cognitive decline in a 4-year follow-up of 1,172 older adults participating in the Epidemiology of Vascular Aging (EVA) study, and that this association was particularly strong among individuals not receiving antihypertensive therapy. Launer and colleagues (Launer, Masaki, Petrovitch, Foley, & Havlik, 1995) reported similar findings during a 20-30 year follow-up of 3,735 middle-

aged adults participating in the Honolulu-Aging Study. Using the same definition to define HTN (SBP > 160/95 mm Hg), participants with HTN were more than twice as likely to exhibit poorer cognitive function relative to their non-hypertensive peers.

Despite the finding that individuals with HTN may have an elevated risk for cognitive decline, the mechanisms by which elevated BP may damage the brain are continuous (Beason-Held et al., 2007), impacting neurocognitive function at subclinical levels among individuals in a dose-response fashion (Waldstein & Katzel, 2001). Many prospective studies have examined increases in BP levels among normo- and prehypertensives as predicting decrements in cognitive function. The majority of observational studies examining this relationship have come from serial investigations from the Framingham Heart Study, finding that elevations in BP, particularly SBP, are associated with decrements in attentional processes, psychomotor skills, and executive functioning, although memory dysfunction also has been noted in some cases (Swan, Carmelli, & LaRue, 1998). Elias and colleagues (Elias, Robbins, & Elias, 1996; Elias, Robbins, Elias, & Streeten, 1998a) demonstrated that higher BP levels are associated with poorer performance on the Wechsler Adult Intelligence Scale (WAIS). In a study of 1,702 unmedicated adults from the Framingham study, Elias and colleagues (Elias, Wolf, D'Agostino, Cobb, & White, 1993) found that both BP levels and chronicity of BP elevation were associated with poorer cognitive performance assessed biannually over a 5-year period. Moreover, Elias noted a graded relationship between reduced BP levels

and improved cognitive performance on a composite variable of attention and memory, which were later replicated in a sample of 1,695 stroke-free individuals (Elias, D'Agostino, Elias, & Wolf, 1995). Other population-based studies have reported similar findings. For example, Singh-Manoux (Singh-Manoux & Marmot, 2005b) found a small but significant relationship between elevations in BP and reduced cognitive performance during 6 and 12-year follow-up assessments of 5,838 middle-aged adults from the Whitehall II study, and this relationship was not attenuated after controlling for cardiovascular risk factors. Similarly, Swan and colleagues (Swan, Carmelli, & La Rue, 1996) found that BP assessed during middle-age predicted lower levels of cognitive performance when 1,173 men participating in the Western Collaborative Group Study were reassessed 25 to 30 years later. More recent studies from Framingham (Elias, Robbins, Elias, & Streeten, 1998b) and the Framingham Offspring Study (Elias et al., 2007) have examined factors that might moderate the BP and cognition relationship, such as type II diabetes mellitus (Elias et al., 1997), as well as hypertensive complications, such as left ventricular hypertrophy (LVH).

There are several factors that may moderate the relationship between HTN and cognitive performance (Waldstein et al., 2001). For example, the chronicity of HTN appears to be an important determinant of the extent of cognitive impairment, with longer duration of high BP associated with greater impairments. In a longitudinal study of 717 participants from the Western Collaborative Group Study, Swan and colleagues

(Swan, Carmelli, & Larue, 1998) demonstrated that those individuals who showed consistently elevated BP assessed in middle age and again thirty years later showed poorer verbal learning and memory performance than participants exhibiting normal BP on both occasions. Although less consistent, recent evidence suggests that gender may also moderate the relationship between HTN and cognition (Waldstein & Katzel, 2004; Singh-Manoux et al., 2005b). For example, Waldstein and colleagues (Waldstein et al., 2004) found that HTN was associated with poorer cognitive performance among older adults in multiple domains, but that this effect was stronger for women compared to men. In contrast, she found that the neurocognitive performance for men with HTN was equivalent to their normotensive counterparts on tasks of working memory. Waldstein and colleagues have also noted that age, education level, and HTN status may be potential moderators (Waldstein, Brown, Maier, & Katzel, 2005). It is unclear whether these factors serve as moderators of the HTN and cognition relationship in the general population.

The relationship between elevated BP and cognitive dysfunction has been expanded in recent years to an investigation of incident dementia, including VaD, AD, and MCI. At the time of this review, more than 20 studies have examined this relationship and findings have varied widely between both dementia endpoints and study methodologies among examinations of the same endpoint. At present, the pattern of findings seem to indicate the high BP predicts incident VaD (Launer et al., 2000;

Skoog et al., 1996; Yoshitake et al., 1995) and undifferentiated dementia (Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005; Freitag et al., 2006) in late-life. HTN also appears to predict incident AD (Skoog et al., 1996; Launer et al., 2000; Kivipelto et al., 2001; Qiu, Winblad, Fastbom, & Fratiglioni, 2003b; Wu et al., 2003; Freitag et al., 2006; Morris et al., 2001), although negative findings have also been reported (Morris et al., 2001).

Four large-scale, prospective studies have demonstrated that higher BP levels are associated with an increased risk of VaD in later life. Launer and colleagues (Launer et al., 2000) reported HTN during midlife was associated with substantially increased risk of both AD and VaD during an approximate 20-year follow-up of 3,703 individuals participating in the Honolulu Heart Program. Interestingly, no relationship between BP and dementia was noted for men undergoing pharmacotherapy with antihypertensive medications. Skoog and colleagues (Skoog et al., 1996) reported similar findings from a population-based study in Sweden. In their study of 382 older adults, participants who exhibited elevated SBP or DBP at age 70 were more likely to develop either AD or VaD during follow-up assessments 10-15 years later. Yoshitake and colleagues (Yoshitake et al., 1995) also found that elevated SBP was associated with VaD among 828 older adults residing in Hisayama, Japan, during a 7-year follow-up. Each 23 mm Hg increase in SBP and 12 mm Hg increase in DBP was associated with a 50% increased risk of VaD. Finally, Yamada and colleagues (Yamada et al., 2003c) found that higher levels of SBP were associated with graded increases in risk for VaD among 1,774 older adults

followed for 25 years. Specifically, every 10 mm Hg increase in SBP was associated with a 33% increased risk of VaD.

Elevated BP has also been shown to predict 'undifferentiated' dementia, although only two prospective studies have demonstrated this relationship. Whitmer and colleagues (Whitmer et al., 2005) examined this association among 8,845 middle-aged adults participating in the Kaiser Permanente Medical Care Program of Northern California. Data on cardiovascular risk factors was collected at middle-age and examined as predicting dementia, assessed at a 30-year follow-up. Specifically, participants with stage 1 HTN (defined as $\geq 140 / 90$ mm Hg) were 25% more likely to develop dementia and this association was not attenuated after controlling for other cardiovascular risk factors including diabetes, high cholesterol, and smoking behavior. Freitag and colleagues (Freitag et al., 2006) conducted a similar study among 2,505 Japanese-American men participating in the Honolulu-Aging study. Higher levels of SBP were associated with graded increases in risk for dementia (either VaD or AD) and this association remained after controlling for cardiovascular confounders. DBP and pulse pressure (PP) were also associated with increased rates of dementia in unadjusted analyses, but these associations were attenuated after controlling for potential cardiovascular confounders.

The association between elevated BP and AD has also been generally positive (Abate, Zito, Ferrari-Ramondo, & Di, 2001), although discrepant findings have also been

reported (Morris et al., 2001). Studies reporting a positive relationship have found that HTN is associated with a two- (Wu et al., 2003) to four- (Launer et al., 2000) fold increased risk of AD among hypertensive patients, relative to normotensives (Kivipelto et al., 2001; Qiu et al., 2003b; Wu et al., 2003; Freitag et al., 2006). Launer and colleagues (Launer et al., 2000) found that HTN at midlife was associated with substantially increased risk of AD in the the Honolulu Heart Program. Similar to the relationship for VaD, elevated SBP or DBP was associated with substantial increases in AD risk. Specifically, individuals with SBP > 160 mm Hg or DBP > 95 mm Hg were four to five times more likely to develop AD over the 20-year follow-up relative to their normotensive peers, but only among individuals who had never been treated using antihypertensive therapy. Wu and colleagues (Wu et al., 2003) reported a similar association among 602 older adults participating in an epidemiologic study in Linxian County, China. Individuals with HTN were twice as likely to develop AD during the 15-year follow-up and trend analyses demonstrated that higher levels of SBP were associated with incident AD in a dose-response fashion.

Although these associations have been relatively consistent across studies (Skoog et al., 1996; Kivipelto et al., 2001; Qiu et al., 2003b; Freitag et al., 2006), several discrepant findings should be noted. As previously described, Yamada and colleagues (Yamada et al., 2003b) found that higher levels of SBP were associated with graded increases in risk for VaD. In their study, the authors also noted a significant univariate relationship

between SBP and AD, comparable to the association observed with VaD. This relationship was attenuated in multivariate analyses, however, with age and education the only predictors remaining significant. These findings have been replicated elsewhere, with HTN predicting VaD, but not AD (Posner et al., 2002). Perhaps more interestingly, Morris and colleagues noted a *negative* relationship between BP levels and incident AD in their prospective study of 634 older adults participating in the East Boston Established Populations for Epidemiologic Studies of the Elderly (EPESE). BP was assessed at multiple time points, both preceding AD diagnosis and at one time-point following AD diagnosis. Analyses demonstrated that BP measured 13 years prior to AD diagnosis was not associated with incident AD, and that higher SBP measured four years prior to diagnosis was protective against the development of AD. Moreover, findings for DBP, although not statistically significant, were similar. Although counterintuitive, these findings have been supported by more recent studies demonstrating that lower BP levels, particularly DBP, may decrease in the years preceding clinical manifestations of dementia and AD, particularly among patients with greater levels of atherosclerosis (Qiu, von, Fastbom, Winblad, & Fratiglioni, 2003a; Qiu, von, Winblad, & Fratiglioni, 2004; Verghese, Lipton, Hall, Kuslansky, & Katz, 2003).

Studies examining the relationship between BP and neurological disorders have been extended in recent years to examine the HBP and MCI relationship. Individuals with MCI experience clinically indicated cognitive dysfunction that does not meet

diagnostic criteria for AD or dementia, although MCI precedes the development of AD for many individuals. Reitz and colleagues (Reitz, Tang, Manly, Mayeux, & Luchsinger, 2007) examined the association between HTN and the development of MCI, which may precede the development of AD. Among the 918 individuals free from MCI at baseline, those individuals with HTN were significantly more likely to develop MCI and amnesic MCI at follow-up. Moreover, HTN was related to the extent of executive function change, a cognitive domain thought to have the greatest vulnerability to BP changes (Qiu, Winblad, & Fratiglioni, 2005; Qiu et al., 2003a). In one of the largest studies to date, Kivipelto and colleagues (Kivipelto et al., 2001) examined the associations between elevated BP, cholesterol, and incident AD among approximately 1,500 individuals participating in the FINMONICA study (Vartiainen et al., 1994). Participants were followed for approximately 21 years, during which time 48 participants developed dementia. Participants with elevated systolic BP at baseline (defined as ≥ 160 mm Hg) were more than twice as likely to develop AD relative to their normotensive counterparts. Notably, participants with elevated cholesterol exhibited similar risk, while participants with both elevated BP and cholesterol were more than three times more likely to develop AD, indicating that the risk of dementia associated with BP may be moderated by other cerebrovascular risk factors.

It is clear from the preceding review that HTN is associated with multiple neurological complications in late-life and represents a major public health burden. Due

to the increased risk of cognitive dysfunction, dementia, and AD associated with HBP, lifestyle intervention studies have begun to examine the effects of exercise and dietary modifications as a means of enhancing cognitive performance.

1.4 HBP Pharmacologic Treatment

Multiple clinical trials have examined the effects of antihypertensive pharmacotherapy in reducing BP and improving cardiac survival. Absolute reductions in BP vary widely between different agents, although established antihypertensive therapies including beta-blockers, angiotensin converting enzyme inhibitors, and diuretics, have all been shown to improve BP control (Chobanian et al., 2003). In addition, clinical trials have demonstrated that antihypertensive therapy is been associated with a 35-40% reduced incidence of stroke, a 20-25% reduced incidence of myocardial infarction (MI), and a > 50% reduction in congestive heart failure (Neal, MacMahon, & Chapman, 2000). Despite the overwhelmingly positive findings of antihypertensive therapy on cardiovascular endpoints, current data examining the protective effects of antihypertensive pharmacotherapy on cognitive impairment and dementia have been inconclusive (McGuinness, Todd, Passmore, & Bullock, 2006; McGuinness, Todd, Passmore, & Bullock, 2008).

1.4.1 Impact of Pharmacologic Treatment on Neurocognition in HBP

Various BP medications have been associated with modest changes in neurocognitive performance, although results have not always been

consistent. Some medications improve performance, while others appear to reduce neurocognitive functioning. In addition, the majority of extant trials examining this relationship were conducted to examine changes in BP and cardiovascular endpoints, collecting cognitive measures as secondary endpoints. The effects of BP pharmacotherapy on cognition are therefore somewhat difficult to ascertain, as the study samples under investigation were heterogeneous with respect to baseline cognitive function, the presence of comorbidities that might affect cognitive function, and age. Considering the methodological shortcomings of the extant literature, it appears that the majority of BP treatments are associated with very little change in cognitive function across a range of domains. Of the few cognitive functions that have been shown to change with treatment, small decrements in complex attentional processes have been observed with diuretic and calcium channel blocker treatment, and small improvements in long-term memory have been observed with beta-blocker treatment (Jonas, Blumenthal, Madden, & Serra, 2001). Individual classes of BP pharmacotherapy are reviewed here briefly by separate classes due to their distinct modes of action.

Beta-Blockers regulate BP by reducing cardiac output and reducing rennin release. Beta blockers have generally been associated with small decrements in many attention-related abilities, but do not appear to have an effect on short-term memory or perceptual skills (Jonas et al., 2001). Studies investigating the effects of beta blockers on

psychomotor function generally report equivocal results, although small decrements in performance have been reported. Despite the equivocal findings in other areas of function, long-term memory appears to improve with beta blocker usage, probably as the result of improved BP control (Jonas et al., 2001), and individuals with AD taking beta-blockers show slower functional decline relative to their non-medicated counterparts (Rosenberg et al., 2008). In addition, the effects of beta blockers do not appear to vary by cardioselectivity or lipid solubility (Blumenthal et al., 1988a).

Angiotensin Converting Enzyme Inhibitors (ACE) inhibitors decrease concentrations of aldosterone, increase bradykinin, and reduce the circulating levels of angiotensin II. ACE inhibitors have generally been found to improve performance on tests of sustained attention, complex attention, and mental flexibility. In contrast, memory performance appears to be unaffected by ACE inhibitor treatment, although one study among older hypertensive women found a positive relationship between ACE inhibitor treatment and improved memory performance (Croog et al., 1994). Perceptual and psychomotor skills have not been extensively studied as they relate to ACE inhibitor treatment, although the few studies that have examined these relationships generally reported equivocal findings (McCorvey E Jr et al., 1993b; Deary, Capewell, Hajducka, & Muir, 1991).

Diuretics may serve as a first line of treatment for HTN or may supplement an existing treatment regimen when target BP levels are not achieved with monotherapy. For this reason, it is difficult to determine whether the cognitive decrements associated

with diuretic usage are the result of medication-specific factors or the severity of HTN of the samples in which this relationship was investigated (Croog et al., 1986). Diuretic usage has generally not been associated with cognitive decrements in the areas of psychomotor skills, memory, and attention, although small decrements in attention have been reported (McCorvey E Jr et al., 1993a). The relationship between diuretic treatment and perceptual skills has not been investigated using randomized designs.

Recent evidence indicates that it may be the intensity of antihypertensive medication administration, not the individual medication per se, that is most predictive of cognitive decrements. Using a prospective cohort design, Agostini and colleagues (Agostini et al., 2007) examined the association between anti-hypertensive medication use and cognitive decrements among 544 community-dwelling hypertensive men, aged 65 years and over. Antihypertensive usage was calculated as both the number of antihypertensive medications and the duration of exposure to medications (i.e. months of administration). Over the course of a one-year follow-up, there was a graded relationship between increasing use of antihypertensive medication and reduced performance on tests of motor and balance, although higher-order cognitive skills, such as executive function, were not impacted.

In addition to observational studies, several recent randomized controlled trials (RCTs) also have investigated the medication and cognition relationship. Muldoon and colleagues (Muldoon, Ryan, Sereika, Flory, & Manuck, 2004) have conducted several

methodologically rigorous studies investigating the effects of anti-hypertensive and lipid-lowering medications on cognitive outcomes. In one study Muldoon and colleagues (Muldoon et al., 2002) investigated the neuropsychological effects of six anti-hypertensive medications in sample of 198 Caucasian men using a randomized, double-blind design with a 2-week wash-out period. Among the 88 men who completed the trial, enhanced performance on tasks of complex sequencing and working memory were observed as a function of medication usage, as well as some improvement on tasks of short-term memory. These results are particularly important given the relatively young age of the sample (mean age = 43 years).

Only one meta-analysis has attempted to combine findings from RCTs in order to quantify the relationship between antihypertensive therapy and cognitive function. Birns and colleagues (Birns, Morris, Donaldson, & Kalra, 2006) examined this relationship by combining data from 16 trials, incorporating data from 19,501 patients. Results varied substantially between different cognitive tests. Modest reductions in BP in a subset of 13,860 patients were associated with improvements in Mini Mental State Examination scores, as well as improved performance on tests of immediate and delayed logical memory performance. In contrast, tests of perceptual processing and learning capacity *worsened* with antihypertensive treatment.

1.4.2 Impact of Pharmacologic Treatment on Dementia in HBP

Four multi-center, randomized, placebo-controlled trials have examined the

effects of antihypertensive medications as a means of protecting hypertensive individuals from the development of dementia in later life (Poon, 2008). Results have varied substantially between studies. Similarly, meta-analytic reviews of RCTs examining this question have differed in their findings based on the inclusion or exclusion of various trials (McGuinness et al., 2006; Feigin, Ratnasabapathy, & Anderson, 2005; Birkenhager & Staessen, 2006).

The Systolic Hypertension in Europe (SYST-EUR) Study was a prospective, double-blind, placebo-controlled study conducted in 19 countries across Europe (Staessen et al., 1997; Forette et al., 1998) incorporating data from over 2,400 individuals. In addition to isolated systolic HTN, study participants were aged 60 years or older and had no history of dementia. The active treatment group received stepwise treatment with nitrendipine, followed by enalapril and/or hydrochlorothiazide. After two years of treatment, active participants showed a 50% reduced incidence of dementia compared with controls. However, due to substantial treatment crossover among the placebo group (27%) due to elevated BP and/or ethical reasons, participants were followed for an additional two years. After 3.9 years of follow-up, active participants exhibited a 55% reduced risk of dementia compared with controls.

The Study of Cognition and Prognosis in the Elderly (SCOPE) trial was a randomized, placebo-controlled trial conducted in Europe, Canada, the United States, and Israel (Lithell et al., 2003). HTN was classified as SBP of 160-179 mm Hg and/or 90-

99 mm Hg DBP. Four thousand nine hundred sixty four individuals aged 70 years or older with an MMSE score of 24 or above participated in the trial. Stepwise treatment was conducted using a sequence of candesartan 8 mg/day, candesartan 16 mg/day, and hydrochlorothiazide 12.5 mg/day. Both active and placebo patients were allowed to receive additional open-label antihypertensive drugs if elevated BP remained after the step-wise treatment. However, open-label treatment excluded ACE inhibitors and angiotensin II receptor blockers. After approximately 44 months of follow-up, no group differences were found in the incidence of dementia or cognitive decline. As with the Syst-Eur study, significant treatment attrition among placebo patients (84%) may have influenced the non-significant findings, although post-hoc analyses among untreated control patients also failed to find significant treatment differences (Lithell et al., 2004).

The Systolic Hypertension in the Elderly Program (SHEP) was a double-blind, placebo-controlled trial conducted in the United States (SHEP Cooperative Research Group, 1991). Participants were aged 60 years or older and had SBP 160-219 mm Hg and < 90 mm Hg, respectively. Over 4,700 patients participated with a mean follow-up duration of 4.5 years. Active treatment consisted of a stepwise treatment of chlorthalidone, atenolol or reserpine. Although a 16% reduction in rates of dementia was observed in treated participants, rates of dementia and cognitive decline did not differ between groups. These results may have been biased by differential rates of attrition, however (Di et al., 2001).

The Heart Outcomes Prevention Evaluation (HOPE) Study was a double-blind, placebo-controlled, randomized trial in which 9,297 patients with vascular disease or diabetes with an additional risk factor were randomly assigned to receive either 10 mg of ramipril, 400 IU of vitamin E, both, or matching placebos for the two-year trial duration. Patients receiving ramipril exhibited reduced SBP (3.8 mm Hg) and DBP (2.8 mm Hg) and had a 32% reduced risk of non-fatal stroke and a 61% reduced risk of fatal stroke. In addition, patients receiving ramipril who did suffer non-fatal stroke during the course of the study were 41% less likely to exhibit residual cognitive decline relative to controls.

Finally, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a double-randomized, placebo-controlled study comprised of 6,105 individuals recruited from 10 different countries (Tzourio et al., 2003). Participants were approximately 64 years of age and had a history of stroke or transient ischemic attack. Patients were followed for approximately 4 years and all were treated with perindopril. In addition, patients without contraindications for diuretics were also treated with indapamide. During an approximate 4-year follow-up, cognitive decline (defined as a 3-point drop on the MMSE) was significantly reduced among treated patients compared with controls [RR = 19% (.04 - .32)]. In contrast, the incidence of dementia did not differ between groups.

Three meta-analyses have attempted to combine findings across RCTs in order to

quantify the relationship between antihypertensive therapy and the development of dementia. In a recent Cochrane review, McGuinness and colleagues (McGuinness et al., 2006; McGuinness et al., 2008) examined the effects of randomized placebo-controlled trials of antihypertensive therapy lasting more than six months on rates of dementia among individuals without cerebrovascular disease. Data from 12,091 participants in the SCOPE, SHEP, and SYST-EUR were combined and overall findings showed that antihypertensive therapy was associated with an 11% reduced rate of dementia, but this effect was not statistically significant (OR = 0.89, 95% CI = 0.69-1.16). Feigin and colleagues (Feigin et al., 2005) reported similar findings in their meta-analysis, demonstrating that antihypertensive therapy was associated with a non-significant 20% (OR = 0.80, 95% CI = 0.63-1.02) reduction in incidence of dementia among individuals with cardiovascular disease. Although neither meta-analysis reported a strong protective effect of antihypertensive therapy on dementia, results appear to vary by the degree of success in lowering BP between treatment and control groups within trials. In their meta-analytic study, Birkenhager and colleagues (Birkenhager et al., 2006) examined this issue by limiting the placebo-controlled RCTs they included to those with > 5 mm Hg reduction in the treatment vs. control groups. Using this methodology, antihypertensive therapy significantly reduced the incidence of dementia by 25% (OR = 0.75, 95% CI = 0.60-0.94) and two antihypertensive therapies appeared to be somewhat more protective: calcium channel blockers and rennin-angiotensin system blockers.

1.5 HBP Non-Pharmacologic Treatment: Diet and Weight Loss

The salutary effects of dietary modification and weight loss on BP have been extensively reviewed (Blumenthal, Sherwood, Gullette, Georgiades, & Tweedy, 2002; Jeffery, 1991; Bacon, Sherwood, Hinderliter, & Blumenthal, 2004; Mulrow et al., 2000). Multiple RCTs have demonstrated that dietary programs are associated with significant BP reductions and may have a synergistic effect when accompanied by reduced weight (Blumenthal et al., 2000; Appel et al., 2003). Among dietary treatments of BP, the Dietary Approaches to Stopping Hypertension (DASH) diet has been most effective (Sacks et al., 1995). The DASH diet is characterized by greater intake of fruits, vegetables, and low-fat dairy foods, modest intake of protein for meat sources, and reduced intake of saturated fat, total fat, and cholesterol. Based on these dietary practices, individuals adhering to the DASH diet should exhibit increased intake of selected minerals (e.g. potassium, calcium, and magnesium) and fiber, as well as decreased intake of macronutrients (e.g. total fat, saturated fat, and protein), all of which have been associated with reductions in BP in epidemiological studies (Sacks et al., 1995).

In the DASH randomized clinical trial (Moore et al., 1999), 459 participants were randomly assigned to one of three groups for the 8-week intervention: a 'typical' American diet (control diet), a "fruits-and-vegetables" diet rich in fruits and vegetables but otherwise similar to the control diet, or a "combination" diet corresponding to the

DASH diet as described above. Both resting systolic and diastolic BPs were markedly reduced among participants in the DASH diet group relative to controls, and the effects of treatment were stronger among individuals with higher BP at baseline. Participants in the “fruits-and-vegetables” group also exhibited modest improvements BP, but not the extent as that observed in the DASH group. Similar findings were observed for ambulatory BP, as reported in a separate paper (Svetkey et al., 1999).

Several important RCTs have examined the effects of combined interventions utilizing dietary components from the DASH diet and established behavioral interventions for BP reduction (i.e. aerobic exercise). One of the largest RCTs to examine this relationship was the PREMIER trial (Appel et al., 2003), a multi-center RCT in which 810 unmedicated adults with high normal BP or stage 1 HTN were randomized to “established” behavioral treatment (i.e. aerobic exercise), “established plus DASH”, and an “advice only” group for 6 months. Participants in both treatment groups exhibited improvements across a range of outcomes relative to “advice only” participants. Specifically, treated participants exhibited improvements in BP, weight, fitness, and improved dietary intake across multiple outcomes. Also consistent with prior studies, participants in the “established plus DASH group” tended to exhibit improved BP and were somewhat less likely to exhibit HTN relative to “established” only participants, although none of these findings achieved statistical significance despite a consistent pattern of findings. The pattern of findings was consistent when examined again during

an 18-month follow-up study, with treated participants exhibiting improvements across a range of cardiovascular endpoints and participants in the “established plus DASH” condition tending to exhibit greater improvements relative to participants in the “established” only condition (Elmer et al., 2006). Blumenthal and colleagues (Blumenthal et al., 2000) conducted a similar RCT examining the effects of an exercise only, combined exercise and weight management program (hereafter referred to as “weight management”), or a control condition on BP and aerobic fitness in a sample of 133 individuals with high normal BP or stage 1 to 2 HTN. Following the 6-month treatment, both the exercise and weight management groups exhibited improvements in BP relative to controls. The weight management group exhibited additional improvements in aerobic fitness relative to the exercise group, including treadmill testing duration, weight loss, glucose and insulin levels, mean arterial pressure, and total peripheral resistance.

Although the effects of weight loss and diet on cardiovascular endpoints have been studied extensively among hypertensive patients, the effects of diet and weight loss on cognitive variables have received far less attention. This is unfortunate given that several prospective studies have demonstrated that diet and weight management may be important factors in the prediction of late-life cognitive disorders (Kretsch, Green, Fong, Elliman, & Johnson, 1997; Brubacher, Monsch, & Stahelin, 2004), despite an inability to demonstrate a clear mechanistic relation (Bryan & Tiggemann, 2001). In

addition, recent evidence indicates that adherence to the DASH diet is associated with reduced risk of coronary heart disease and stroke, and that this relationship is more pronounced among individuals with a history of HTN (Fung et al., 2008). Several randomized and quasi-randomized trials have investigated the effects of weight loss and dietary modification among individuals with HTN as a behavioral treatment to preserve cognitive function. Although results vary somewhat between studies, few studies have reported cognitive improvements associated with diet and weight loss changes.

1.5.1 Impact of Diet and Weight Loss on Neurocognitive Function

The relationship between diet and cognitive function has been a topic of increasing interest over the past two decades, as numerous studies have shown that variations in dietary practices and nutrient intake are predictive of cognitive decline (Del, Panza, Capurso, & Solfrizzi, 2006), dementia (Luchsinger & Mayeux, 2004), and AD (Essink-Bot, Pereira, Packer, Schwarzsinger, & Burstrom, 2002). The role of healthy dietary practices in the prevention of late-life cognitive dysfunction carries major public health implications, as the World Health Organization (WHO) predicts that 29 million individuals living with dementia by the year 2020 (Rice et al., 2001; Haan & Wallace, 2004), accompanied by an estimated 83% increase in associated health care costs for individuals with AD. Various dietary practices and specific nutrient components of these diets have been examined in relation to cognitive performance. Although the existing literature on this subject is extensive, extant investigations have focused on the

following components of diet as either protecting against cognitive decline or enhancing neurocognition: 1) dietary fatty acids (including fish oil) and the Mediterranean diet, 2) antioxidants (including vitamins E and C), as well as fruits and vegetables, 3) vitamin B6, B12 (cobalamin), and folate, and 4) caloric restriction. The relationship between alcohol consumption and cognitive function has been reviewed in detail elsewhere (Meister, Whelan, & Kava, 2000).

1.5.1.1 Dietary Fatty Acids

Dietary fatty acids are classified by two general subtypes: saturated fatty acids and unsaturated fatty acids. Among these subtypes, unsaturated fatty acids may be further divided into monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs). Saturated fatty acids are derived primarily from meat and dairy products, but also from cookies and pastries. An important component of dietary fat consumption is the levels of n-3 and n-6 PUFAs, commonly referred to as omega-3 and omega-6 fatty acids. n-3 PUFAs are primarily derived from fish and marine sources and consist of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), whereas n-6 PUFAs are primarily derived from legumes, nuts, and other plant-based sources and consist of α -linolenic acid (ALA).

Multiple prospective studies have examined the relative intake of these dietary components and subsequent cognitive dysfunction. The majority of extant studies have reported a similar pattern of findings: greater fat intake is associated with *greater* risk of

cognitive dysfunction and dementia, whereas greater intake of n-3 relative to n-6 fatty acids is associated with *lesser* risk of these outcomes. Results have also been relatively consistent across outcomes, with studies examining changes in cognitive function reporting similar findings to those studies examining the incidence of MCI, VaD, AD, and other types of dementia.

Prospective studies have generally examined the effects of diet in protecting age-related cognitive decline among non-demented samples. Although several studies have utilized extensive test batteries assessing multiple cognitive domains, the majority of extant studies have examined changes in mental status, as indexed by the MMSE. In an early population-based study from the Zutphen Elderly Study, Kalmijn and colleagues (Kalmijn, Feskens, Launer, & Kromhout, 1997) examined the association between intake of linoleic PUFAs and fish consumption and subsequent cognitive decline and cognitive impairment among 476 men aged 69-89 years. Higher levels of linoleic PUFAs and fish consumption were shown to protect against incident cognitive impairment and cognitive decline, defined by performance on the MMSE. In addition, these findings were strengthened by the studies control of other confounding dietary elements, including total energy intake, alcohol consumption, as well as dietary intake of beta-carotene, vitamins C and E, and flavanoids, none of which were protective against cognitive dysfunction. In a subsequent study from Zutphen, van Gelder and colleagues (van Gelder, Tijhuis, Kalmijn, & Kromhout, 2007) found that elderly men who consumed

greater amounts of fish were significantly less likely to exhibit cognitive decline relative to men who did not consume fish. In addition, greater fish consumption appeared to protect against cognitive decline in a dose-response fashion. Capurso and colleagues (Capurso et al., 1997) reported similar findings in a prospective study of 278 individuals, followed for approximately 9 years. Examination of changes in MMSE performance demonstrated that individuals with high PUFA (> 220 kJ / day) and MUFA intake (> 2000 kJ / day) were less likely to exhibit cognitive decline relative to individuals with low intake.

Although the majority of existing studies have utilized self-reported dietary practices to index consumption, Heude and colleagues (Heude, Ducimetiere, & Berr, 2003) examined the association between PUFAs and cognitive decline by examining the fatty acid consumption of erythrocyte membranes from blood samples in 246 subjects participating in the Etude du Vieillissement Arteriel (EVA) cohort study. Although approximately 1,400 subjects participated in the larger cohort study, financial restrictions imposed by erythrocyte assays limited the number of individuals included in this analysis. An inverse association was noted between the ratio of n-3 and n-6 PUFA in erythrocyte membranes and MMSE performance. Specifically, a higher proportion of n-3 PUFAs was associated with a 40% reduced risk of moderate cognitive decline, defined as a decline of two or more points in MMSE performance. Similarly, Dullemeijer and colleagues (Dullemeijer et al., 2007) examined the relationship between

n-3 PUFA plasma levels and cognitive decline in a 4-year follow-up of older individuals participating in the FACIT study. Greater plasma n-3 PUFA levels were associated with protection against declines in performance for sensorimotor and complex speed, although memory, information-processing, and word fluency did not appear to be impacted.

In one of the largest studies to date to examine the role of fatty acids in cognitive decline, Morris and colleagues (Morris, Evans, Bienias, Tangney, & Wilson, 2004) examined the relationship between saturated and trans-unsaturated fat in predicting cognitive decline among 2,560 individuals participating in the Chicago Health and Aging Project. Notably, the individuals in this trial were relatively at baseline, as the exclusion criteria for this trial eliminated individuals with a history of stroke, heart disease, or diabetes at baseline. Cognitive decline was assessed using a more comprehensive neuropsychological test battery, which included the East Boston Tests of memory, the MMSE, and the Symbol Digit Modalities Test. Examination of 6-year changes in cognitive function indicated that individuals with higher dietary intake of saturated or trans-unsaturated fats or low nonhydrogenated unsaturated fats were associated with a greater incidence of cognitive decline.

Although studies have varied widely in their exclusion criteria and analytic control of CVRFs, Beydoun and colleagues (Beydoun, Kaufman, Satia, Rosamond, & Folsom, 2007) conducted a notable study in which individuals from the Atherosclerosis

in Communities Study (ARIC) who were either hypertensive or dyslipidemic were analyzed as an at-risk group. In these 2,251 subjects aged 50 years and older were examined at three time points, spanning twelve years. Consistent with previous findings, those individuals with higher plasma levels of n-3 PUFAs were less likely to exhibit decline on cognitive measures of verbal fluency, although these individuals did not exhibit improved performances on measures of delayed memory or psychomotor speed.

In contrast to the assessment of cognitive decline, prospective studies examining the relationship between dietary practice and the development of dementia have typically relied on cognitive performance in conjunction with a clinician diagnosis of dementia. In some cases this data is supplemented with MRI results, when available. In addition to their work on cognitive decline, Kalmijn and colleagues (Kalmijn et al., 2004) have also demonstrated that the protective effects associated with modest dietary fat consumption and greater fish consumption on dementia. In their study of 5,386 non-demented individuals from the Rotterdam study followed for approximately 2 years, the authors found that greater dietary intake of total fat, saturated fat, and cholesterol were all predictive of incident dementia and were most strongly associated with reduced risk of VaD. Similar to their previous study, greater fish consumption was protective against the development of dementia. In contrast to their findings for dietary fat, fish consumption appeared to be most protective against the development of AD. Barbege-

Gateau and colleagues (Barberger-Gateau et al., 2002) also found a protective effect of greater fish consumption among 1,674 older adults aged 68 and over participating in the PAQUID (Personnes Agees QUID) cohort study. Specifically, individuals with greater fish consumption were less likely to develop AD over the 2-7 year follow-up in age and sex-adjusted analyses. Interestingly, this relationship was somewhat attenuated following adjustment for education level and, in contradiction to previous findings, greater meat consumption was not predictive of subsequent dementia. Morris and colleagues (Morris et al., 2003b; Morris et al., 2003a) have recently conducted several studies examining the effects of diet on the incidence of AD. In both studies, 815 subjects from the Chicago Health and Aging project were followed for approximately 4 years, during which 131 sample participants developed AD. Consistent with previous findings, higher intake of saturated and trans-unsaturated fats were associated with a higher risk of AD, whereas higher intake of n-3 and n-6 fatty acids were associated with a lower risk. Finally, Schaefer and colleagues (Schaefer et al., 2006) examined the relationship between omega fatty acids and incident dementia among 899 older men and women. The authors examined plasma levels of decosahexaenoic acid phosphatidylcholine (DHA-PC) levels in relation to incident dementia during an approximate 9-year follow-up. Subjects with higher DHA-PC levels (i.e.in the highest quartile) were 47% less likely to develop AD relative to other individuals.

Solfrizzi and colleagues (Solfrizzi et al., 2006) have extended these findings,

examining the relationship between PUFA intake and the development of MCI among 464 non-demented older adults participating in the Italian Longitudinal Study of Aging. During an approximate 3-year follow-up of participants, higher intake of PUFAs appeared to protect against the development of MCI. However, this relationship was attenuated following adjustment for possible confounders. Given the small sample size of individuals who developed MCI in this study (n=18), the protective effects of PUFAs for MCI remain to be elucidated.

Although the results of longitudinal studies have been generally consistent, important negative findings also warrant attention. Engelhart and colleagues (Engelhart et al., 2002b), in a subsequent analysis of individuals from the Rotterdam study, failed to find an association between high intake of total fat, saturated fat, trans fats, cholesterol, and the subsequent development of dementia. In contrast to the Kalmijn study, this analysis utilized a longer follow-up period (6 years instead of 2). In addition to the negative findings for dietary fat intake, consumption of fatty acids did not appear to protect against the development of dementia. At present these discrepant findings have yet to be reconciled.

Although pilot studies of omega-3 fatty acids reported cognitive benefits with fish oil supplementation, well-controlled RCTs of omega-3 fatty acids have yielded similarly equivocal findings (Scarmeas et al., 2009). Yehuda and colleagues (Yehuda, Rabinovtz, Carasso, & Mostofsky, 1996), in an early study, examined whether a

combination of n-3 and n-6 fatty acids might improve cognition and quality of life among 100 AD patients. In their double-blind, 4-week study, patients demonstrated modest improvements in short-term memory and quality of life measures. In a 24-week, double-blind pilot study, Chiu and colleagues (Chiu et al., 2008) examined the effects of omega-3 PUFA monotherapy in improving cognitive performance among 46 patients with either AD or MCI relative to placebo controls. Results showed that, among participants completing at least one post-treatment follow-up assessment (76%), treatment group participants showed improvement in the Clinician's Interview-Based Impression of Change Scale (CIBIC-plus). In addition, comparison of individuals with MCI showed that those on omega-3 PUFA monotherapy exhibited cognitive benefits on the AD Assessment Scale (ADAS-cog) relative to individuals with MCI in the placebo condition. These findings were not significant among individuals with AD, however. Terano and colleagues (Terano et al., 1999) reported significant improvements in cognition following DHA supplementation among twenty elderly adults with VaD. Participants were randomly assigned to receive 0.72 g/day DHA daily for one year, whereas control participants continued their dietary practices as usual. Cognitive function was assessed every three months by MMSE performance and Hasegawa's dementia rating scale. At three and six months, the treatment group exhibited improved cognitive function as indexed by Hasegawa's dementia rating scale, and this improvement was significantly correlated with serum levels of DHA. After twelve

months of treatment, however, these differences were no longer significant.

Despite the positive findings of these pilot studies, large-scale RCTs have failed to find a benefit to fish oil in staving off cognitive decline and/or dementia among adults. In a randomized, double-blind, placebo-controlled trial, van de Rest and colleagues (van de et al., 2008) found no effects of omega-3 supplementation among 321 healthy adults, aged 65 years and older. In their study, participants were assigned to a 26-week treatment in which they received 1,800 mg/day, 400 mg/day, or placebo capsules. Prior to treatment and again following the 26-week protocol, participants completed an extensive neuropsychological test battery, including measures of attention, sensorimotor speed, memory, and executive function. Despite substantial increases in plasma concentrations of EPA + DHA, neither of the treatment groups exhibited improvements in cognitive performance. Finally, in a 6-month randomized controlled trial of n-3 supplementation, Freund-Levi and colleagues (Freund-Levi et al., 2006a) reported similar results among 204 patients with AD. After 6-months of treatment, the groups did not differ in cognitive performance, although sensitivity analyzes revealed that individuals with very mild impairment (i.e. MMSE > 27 points) exhibited modest cognitive benefits.

1.5.1.2 Mediterranean Diet

Although the specific components of fatty acid intake remain to be elucidated, recent studies have examined the role of dietary practices that emphasize these

components as strategies to prevent dementia. Accordingly, the Mediterranean diet has received substantial attention due to its focus on fish intake, vegetables, legumes, fruits, cereals, and unsaturated fatty acids (Balk et al., 2007; Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006). In addition, this diet is characterized by a low intake of dairy products, meat, and saturated fatty acids, as well as regular, modest intake of alcohol. Recent evidence indicates that the Mediterranean diet is associated with reduced risk of MCI and AD and that greater adherence to this diet may protect against subsequent cognitive dysfunction in a dose-response fashion (Scarmeas, Stern, Mayeux, & Luchsinger, 2006).

In a study of 2,258 community-dwelling, nondemented New Yorkers, Scarmeas and colleagues (Scarmeas et al., 2006) examined the association between adherence to the Mediterranean diet and subsequent development of AD during an approximate 4-year follow-up. Greater adherence to the Mediterranean diet was associated with dose-response protection from developing AD. Notably, compared to individuals in the highest quartile of dietary adherence, individuals with poor Mediterranean dietary practices had an approximately 40% greater risk of developing AD. Interestingly, these results were unchanged in a subsequent study among the same cohort when measures of vascular functioning were accounted for, leading the authors to conclude that the observed relationship between dietary fat and AD is not mediated by vascular health (Scarmeas et al., 2006).

These findings were recently extended to demonstrate that Mediterranean diet adherence is associated with protection against incident MCI in a similar fashion. Scarmeas and colleagues (Scarmeas et al., 2009) recently examined this relationship in a similar sample of 1,393 New Yorkers over an approximate 5-year follow-up. Results were similar to the relationship observed with AD: greater adherence to the Mediterranean diet was associated with dose-response protection against incident MCI. Specifically, for every one-unit increase in the authors' Mediterranean diet adherence score, the risk of subsequent MCI was reduced 8%.

1.5.1.3 Antioxidants

Antioxidants are found naturally in foods and can also be taken as supplements. Greater antioxidant intake is hypothesized to prevent age-related neurologic dysfunction because brain tissue contains low levels of endogenous antioxidants and is therefore particularly vulnerable to free-radical damage (Reiter, 1995; Del et al., 2006). Moreover, oxidative stress has been implicated as one of the primary mechanisms of age-related neuronal decline (Valko et al., 2007; Nunomura et al., 2006). Accordingly, there has been great interest in the role of antioxidants in the prevention of age-related cognitive decline and the development of neurocognitive disorders.

Early studies of antioxidants emerged from uncontrolled observational trials in which greater consumption of fruits and vegetables were shown to be associated with better cognitive function (Ortega et al., 1997) and reduced incidence of ischemic stroke

(Joshiyura et al., 1999). Ortega and colleagues (Ortega et al., 1997), for example, demonstrated that high intakes of fruit, folate, carbohydrate, thiamine, and vitamin C were associated with reduced rates of cognitive impairment among 260 elderly individuals, aged 65 to 90 years. Morris and colleagues (Morris, Evans, Tangney, Bienias, & Wilson, 2006) extended these findings, noting that greater intake of vegetables, but not fruits, was associated with improved cognitive performance among 3,718 older adults participating in the Chicago Health and Aging Study, and this effect was not attenuated after controlling for cardiovascular comorbidities. In an attempt to examine the components of diet that are most protective against cognitive decline, Morris and colleagues (Morris, Evans, Bienias, Tangney, & Wilson, 2002) examined the relationship between vitamin E use and cognitive decline among 2,889 older adults (aged 65 years and above) from the same cohort. Participants completed cognitive assessments at baseline and again 18 months later. Cognitive function was indexed by using a composite score derived from four cognitive tests that assessed memory, mental status, and psychomotor speed / executive function. The study was strengthened by its careful control of confounding variables, including other dietary factors such as carotene and vitamin C. Results revealed a dose-dependent protective effect of vitamin E intake, either from diet or supplement use, and lower rates of cognitive decline. Secondary analyses revealed that the protective effects of vitamin E were strongest among individuals with higher intakes of vitamin E from dietary sources relative to individuals

with low vitamin E dietary consumption taking supplements. Interestingly, vitamin C was not protective against cognitive decline in this study.

Masaki and colleagues (Masaki et al., 2000) have examined the effects of vitamin E and C supplementation specifically in protecting cognitive function and reducing risk for the development of VaD, stroke, and AD. In their examination of 3,385 men participating in the Honolulu-Asia Aging Study, use of either vitamin C or E was associated with better cognitive performance when participants were assessed 6-8 years later. Participants who were taking both vitamin C and E tended to exhibit better cognitive performance than individuals taking only one of these supplements. In contrast, individuals taking both supplements were less likely to develop VaD, and mixed/other dementias, although the use of supplements did not appear to protect against the development of AD.

Although the relationship between antioxidant supplements and AD has been less conclusive, dietary intake of antioxidants appears to protect against incident AD. Engelhart and colleagues (Engelhart et al., 2002a) examined this among 5,395 individuals participating in the Rotterdam study, 197 of whom had developed AD after 6 years of follow-up. Among the dietary factors assessed, higher intake of vitamins C and E were associated with dose-dependent reductions in risk for AD and this relationship was strongest among current smokers. In addition, current smokers with higher intakes of beta carotene and flavanoids showed lower rates of AD, although these

factors did not appear to be protective among non-smoking participants. This study was strengthened by its careful control of confounding variables including the use of antioxidant supplements, presence of carotid plaques, total energy intake, and baseline MMSE performance. La Rue and colleagues (La et al., 1997) reported similar findings in an examination of 137 older adults participating in the New Mexico Aging Project Study. Nutritional status was assessed at a baseline exam and again 6 years later. At the 6-year assessment, a comprehensive neuropsychological exam was administered, assessing visuospatial performance, abstract reasoning, and memory. Examination of simple correlations between dietary and cognitive variables revealed several interesting associations. Higher past intake of vitamins E, A, B-6, and B-12 were associated with better performance on abstractions tests and visuospatial recall. In addition, higher levels of thiamine, riboflavin, niacin, and folate were associated with better abstraction. In contrast, higher plasma ascorbate levels were associated with better visuospatial performance. Vitamin supplementation use was also associated with several tests of visuospatial and abstraction abilities.

Flavonoids, phenolic compounds abundant in red wine and various types of berries, have also been examined due to their antioxidant effects on low density lipoprotein (LDL). In an examination of 1,367 older adults participating in the PAQUID cohort study, Commenges and colleagues (Commenges et al., 2000) found that individuals consuming higher levels of flavonoids were approximately 50% less likely to

develop dementia during a 5-year follow-up. Letenneur and colleagues (Letenneur, Proust-Lima, Le, Dartigues, & Barberger-Gateau, 2007) extended these findings by examining the 10-year follow-up from PAQUID, demonstrating that individuals with higher flavonoid intake showed the least age-related decline in cognitive performance, as indexed by the MMSE. Although few prospective studies have investigated the protective effects of flavonoids on cognitive function, there is abundant laboratory data among animals supporting possible mechanisms for this protective relationship (Youdim, Shukitt-Hale, & Joseph, 2004).

Several RCTs have investigated the effects of Vitamin E and/or C supplementation in the prevention of dementias, such as AD. In the most comprehensive review of these trials to date, Isaac and colleagues (Isaac, Quinn, & Tabet, 2008) examined the effects of vitamin E in the treatment and prevention of AD and MCI. Based on their comprehensive literature search, only two trials met inclusion criteria, incorporating data from two studies, one among AD patients (Petersen et al., 2005) and the other among individuals with MCI (Sano et al., 1997). In their study of 341 patients with AD of moderate severity, Sano and colleagues (Sano et al., 1997) examined the effects of selegiline, alpha-tocopherol, or placebo in slowing the progression of AD over a two-year period. Specifically, survival analyses were used to assess the effects of medication on extending the time before a composite end-point of death, institutionalization, or loss of the ability to perform at least two of three basic activities

of daily living, as indexed by the Blessed Dementia Scale. Patients on either medication or a combination of both showed slowed rates of cognitive decline relative to individuals in the placebo group. In their study of 769 individuals with MCI, Peterson and colleagues (Peterson et al., 2005) examined whether the administration of either vitamin E supplements or Donepezil might slow the progression to AD. Although neither treatment group appeared to benefit from therapy after 3 years of follow-up, pre-planned analyses every 6-months demonstrated that both treatments showed a slower rate of conversion to AD during the first year of treatment and that this effects was most pronounced among individuals with the APOE-4 genotype. Taken together, current findings from RCTs indicate that antioxidant supplementation may confer small benefits among populations vulnerable to dementia, slowing the rate of disease progression. The effects of antioxidants among healthier samples remain unclear, however.

1.5.1.4 Vitamins B6, B12 (cobolamine), and Folate

Multiple population-based observational studies have examined the relationship between intake of vitamins B6, B12, and folate as protective against neurocognitive decline and are reviewed elsewhere (Van & Sano, 2007). Although a multitude of observational studies have examined this question, results have been mixed, with many studies reporting protective effects and others finding equivocal associations. Among individuals participating in the Kungsholmen Project, a population-based longitudinal study in Sweden, Wang and colleagues (Wang et al., 2001) examined the association

between serum levels of B12 and folate among non-demented, older adults (aged 75 years or greater). Among the 350 participants followed for approximately three years, lower levels of either B12 or folate were associated with a greater than two-fold increase in the risk of developing AD, and these associations were even stronger among individuals with higher baseline cognitive function. Morris and colleagues (Morris et al., 2006) relationship among 1,041 residents participating in the Chicago Health and Aging Project. Participants were aged 65 or greater and were followed for approximately 4 years. Dietary intake was assessed using self-reported food frequency practices, indexed by the Food Frequency Questionnaire. After controlling for demographic factors, cognitive activities, APOE-4, and other dietary factors such as vitamin E and niacin, neither self-reported B6, B12, or folate intake were predictive of incident dementia. Most recently, Luchsinger and colleagues (Luchsinger, Tang, Miller, Green, & Mayeux, 2007) examined this association among 965 Manhattan residents, through a random sampling of Medicare recipients aged 65 years or older. Individuals with the highest intake of folate exhibited a 50% lower rate of AD compared to participants with lesser intakes. Notably, this association remained significant after controlling for total energy intake, cardiac comorbidities, and APOE-4 genotype. Interestingly, neither self-reported B6 nor B12 intake appeared to protect against the development of AD.

Few large-scale, well-controlled RCTs have examined the effects of either

vitamins B6 or B12 on cognitive function, despite a plethora of observational studies in which these nutrients have been examined. In a systematic review of RCTs, Balk and colleagues (Balk et al., 2007) examined the value of B6, B12, and folate supplementation on cognitive function. Fourteen trials were initially identified, reporting on data from approximately 50 different tests of cognition. Existing studies were marked by small sample sizes, heterogeneity in outcomes, and a lack of data on clinical outcomes related (eg conversion to dementia). Three trials of vitamin B6 and six trials of B12 were available for analysis. None of the available interventions reported cognitive benefits associated with supplementation across a variety of doses, modes of administration, and various populations. Three trials examined the effects of folic acid, only one of which reported a benefit in cognitive function among individuals with cognitive impairment and low baseline serum folate levels. Interestingly, six trials that utilized combinations of B vitamins all concluded that the interventions had no effect on cognitive function and, among these, half reported that the placebo arm outperformed treatment participants on several cognitive tests.

Three Cochrane collaboration reports lend further credence to these findings. In a systematic literature review, Malouf and Grimley (Malouf & Grimley, 2008) examined the effects of folate supplementation with and without B12 in the maintenance of cognitive function, as well as the prevention and treatment of dementia. Eight RCTs met inclusion criteria: four among healthy, older adults and four among participants with

mild to moderate cognitive impairment or dementia with or without diagnosed folate deficiency. Two of these studies utilized a combination of folic acid and vitamin B12 and the majority of existing studies were successful in boosting B12 levels and, accordingly, reducing homocysteine concentrations. Among healthy, older adults, there was no consistent evidence that folic acid supplementation with or without vitamin B12 improved cognitive function. The one notable exception was a decidedly positive trial by Durga and colleagues (Durga et al., 2007c) that examined this relationship among otherwise healthy elderly adults with elevated homocysteine levels at enrollment. Interestingly, previous RCTs among individuals with elevated homocysteine did not demonstrate cognitive gains (McMahon et al., 2006). Similarly, the majority of extant trials among individuals with cognitive impairment have failed to demonstrate a benefit in cognitive function with supplementation. Again, a notable exception was a pilot trial among individuals with AD (Connelly, Prentice, Cousland, & Bonham, 2008), in which folic acid supplementation of 1 mg/day improved overall response to cholinesterase inhibitors, resulting in cognitive gains in Instrumental Activities of Daily Living and Social Behavior indices. A separate Cochrane database review conducted by Malouf and Sastre (Malouf & Areosa, 2003) reported similar findings in an examination of the effects of B12 on cognition, specifically. Three trials were included, all of which examined this association among individuals with cognitive impairment and low levels of serum B12. None of existing trials reported beneficial effects of B12 supplementation

on cognitive function across patient groups and modes of administration.

Malouf and Grimley (Malouf & Grimley, 2003) have also examined the effects of B6 on cognitive function among both healthy, older adults as well as individuals with cognitive impairment and dementia. In their Cochrane review, the authors reported that few RCTs had examined the effects of B6 among older adults and that none had examined these effects among individuals with cognitive impairment. Among the two trials included in their review, neither demonstrated an effect of B6 supplementation on cognitive function. More recently, Kang and colleagues (Kang et al., 2008) examined the effects of B6, B12, and folic acid among 2,009 women aged 65 years and older with CVD or ≥ 3 cardiovascular risk factors participating in the Women's Antioxidant Cardiovascular Study. Results showed that the trial was largely ineffective in delaying cognitive decline, but that a subgroup of women with low B vitamin levels at baseline demonstrated modest cognitive benefits. Taken together, the vast majority of existing trials have failed to find a benefit of B6, B12, or folate supplementation on cognitive function.

1.5.1.5 Caloric Restriction

Recent evidence indicates that lower levels of caloric intake may be associated with improved cognitive performance and reduced rates of dementia. Although several recent examinations have been conducted in humans, this relationship has been studied extensively among animals (Martin et al., 2007). Luchsinger and colleagues (Luchsinger,

Tang, Shea, & Mayeux, 2002) examined this relationship among 980 older adults participating in the Washington Heights-Inwood Columbia Aging project. Participants completed a food frequency questionnaire and were then followed yearly to assess for new-onset dementias. Greater caloric intake was associated with a graded increase in risk of AD and this relationship was particularly strong for individuals with the APOE-4 genotype. Although greater dietary fat intake tended to be associated with increased risk of AD, this relationship did not reach statistical significance.

Willcox and colleagues (Willcox et al., 2007) examined the relationship between low caloric intake and neurological function by conducting a retrospective analysis of 54 Okinawans, a population marked by 'successful' aging with a high prevalence of centenarians and low rates of dementia. Participants were recruited from the Okinawa Centenarian Study, an ongoing population-based study of Okinawas over the age of 100 that began in 1976. Archival data from annual physical examinations and dietary data were examined as predictors of current functioning. As a reference group, control participant data was selected from the NHANES I trial in order to provide a normative population reference. Relative to control subjects, Okinawans exhibited dietary patterns characterized by markedly low caloric intake and, accordingly, extremely low BMI (eg < 21 kg /m²). Indeed, during their 30s, the average Okinawan reported a daily energy intake of 1785 kcal/day and a daily energy expenditure of 2003 kcal / day, representing a 10.9% energy *deficit*. This pattern was relatively consistent during other decades of life

and the majority of Okinawans studied reported continued caloric restriction and exhibited similarly low BMIs during later life. Although this study provides ancillary data demonstrating that caloric restriction may protect against age-related decline, it should be noted that little empirical data are available from this population demonstrating a causal relationship between low caloric intake and protection against age-related decline.

Several recent RCTs have examined the effects of caloric restriction in enhancing cognitive function. Witte and colleagues (Witte, Fobker, Gellner, Knecht, & Floel, 2009) recently examined the effects of caloric restriction on cognitive performance among fifty healthy, elderly subjects at either normal weight or mildly overweight. Participants were randomly assigned to either caloric restriction, intake of unsaturated fatty acids (UFAs), or a control condition. Following three months of treatment, individuals in the caloric restriction group exhibited increased verbal memory scores and these improvements were correlated with decreased levels of fasting insulin and C-reactive protein. Notably, these results were strongest among subjects with the best adherence. Serum levels of brain derived neurotrophic factor (BDNF), a growth factor thought to mediate the effects of aerobic fitness on brain function, were also assessed in this trial, but were not altered with treatment and did not correlate with changes in cognitive performance.

Martin and colleagues (Martin et al., 2007) conducted a similar study among 48

overweight adults, aged 25 to 50 years. Participants were randomly assigned to one of four groups: caloric restriction, caloric restriction and exercise, a low-calorie diet condition, or to a control group (weight maintenance). At baseline, 3 months, and again at 6 months, cognitive tests were administered assessing verbal and visual memory, as well as concentration/attention. Overall, cognitive function changed very little across any group and no consistent pattern of change emerged. In addition, changes in cognitive performance were not related to changes in caloric intake (indexed by daily energy deficit) or weight loss.

Bryan and Tiggemann (Bryan et al., 2001) conducted a quasi-randomized study of 63 overweight women participating in a 12-week dietary intervention. Participants in the treatment group undertook a 12-week, 15% fat, weight reducing diet. The diet was designed to produce a 20% energy deficit resulting in a 10-12 kg weight loss over the course of the study. Neuropsychological tests were administered before and following treatment, assessing a wide range of functions including speed of processing, executive function, working memory, and recall abilities. Psychological well-being was also assessed. Although psychological well-being improved throughout the study, only 1 of the 15 neuropsychological tests (Free Recall Intrusions) administered was significantly improved in the treatment group relative to controls, indicating that weight loss was not associated with cognitive gains.

Halyburton and colleagues (Halyburton et al., 2007) conducted a randomized

trial among 93 overweight or obese men and women comparing the cognitive effects of a low-carbohydrate, high-fat diet (LCHF) with a conventional high-carbohydrate, low-fat (HCLF) diet. Following the 8-week intervention, LCHF participants exhibited greater weight loss relative to controls. In contrast, no treatment differences were observed on tasks of working memory, as both groups showed comparable improvements. Although speed of information processing improved among HCLF participants relative to the LCHF group, these improvements were relatively small and thus interpreted as practice effects.

1.6 HBP Non-pharmacologic Treatment: Aerobic Exercise

Higher levels of physical fitness have consistently been associated with lower BP and reduced incidence of HTN both prospectively (Hu et al., 2004) and in RCTs (Blumenthal et al., 2000), which have been reviewed elsewhere (Halbert, Silagy, Finucane, Withers, & Hamdorf, 1999b; Halbert et al., 1997; Fagard & Cornelissen, 2007). Several large-scale, prospective studies have demonstrated that greater levels of aerobic exercise are associated with reduced BP, including 7,685 University of Pennsylvania alumni (Paffenbarger, Jr., Thorne, & Wing, 1968), 14,998 Harvard alumni (Lee, Hsieh, & Paffenbarger, Jr., 1995), and 6,039 self-referred normotensives clinical patients (Blair, Goodyear, Gibbons, & Cooper, 1984). RCTs have reported similar findings, noting that both systolic and diastolic BP are reduced with aerobic exercise training, although the magnitude of this effect varies between analyses (Halbert, Silagy, Finucane, Withers, &

Hamdorf, 1999a; Halbert et al., 1997; Fagard et al., 2007; Whelton, Chin, Xin, & He, 2002; Blumenthal et al., 2002; Kelley & Tran, 1995; Kelley & Kelley, 1999; Kelley, 1999; Kelley, Kelley, & Tran, 2001; Kelley & Sharpe, 2001). In a recent meta-analysis of 72 RCTs, Fagard and Cornelissen (Fagard et al., 2007) found that aerobic exercise training was associated with net reductions of approximately 3 mm Hg in combined results across samples, and this effect was stronger among hypertensive samples. Improvements in BP were accompanied by improved vascular resistance, plasma norepinephrine, plasma rennin activity, and anthropomorphic indices such as weight and percentage body fat. Current evidence therefore indicates that BP may be reliably reduced with regular aerobic exercise and these findings are strengthened by the consistency of findings and breadth of patient populations in which the beneficial effects of exercise have been demonstrated.

1.6.1 Aerobic Exercise Effects on Neurocognition

Despite the breadth of studies demonstrating that aerobic exercise improves BP, few studies have examined whether reducing BP by exercising is associated with improvements in cognitive function. In an attempt to investigate this relationship, Cerhan and colleagues (Cerhan et al., 1998) examined the association between HTN status, FEV₁, and cognitive performance among 14,000 middle-aged adults participating in the Atherosclerosis Risk in Communities Study. Although cross-sectional, HTN status was associated with poorer cognitive performance and this effect remained

significant after controlling for multiple confounders, including level of aerobic fitness (indexed by FEV₁). Barnes and colleagues (Barnes, Yaffe, Satiriano, & Tager, 2003) found a similar relationship between fitness and cognition in a prospective 6-year follow-up of 349 individuals free from cardiovascular or cognitive co-morbidities at baseline. Higher levels of cardiorespiratory fitness at baseline exhibited more rapid cognitive decline relative to their healthier counterparts, and these effects persisted after controlling for other factors, including HTN status. In addition, studies among individuals with AD tend to report cognitive benefits associated with exercise, regardless of presence of risk factors across trials (Barnes et al., 2003). Taken together, these findings provide preliminary evidence that aerobic fitness may be associated with improved cognitive performance independent of its effect on BP, although this relationship has yet to be examined in the context of a controlled trial.

Although the relationship between BP reduction through exercise and neurocognitive change has yet to be studied rigorously, the relationship between physical activity and cognitive function has been reviewed extensively over the past decade (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Heyn, Abreu, & Ottenbacher, 2004). Despite multiple observational and interventional studies, there has been little consensus as to whether physical activity enhances cognitive function (Angevaren et al., 2008; Colcombe & Kramer, 2003a). Previous meta-analytic studies have demonstrated that aerobic exercise training is associated with improved cognitive

function in multiple cognitive domains among older adults (Colcombe et al., 2003a). More recent studies, however, have failed to replicate these findings, demonstrating that improved aerobic fitness through exercise training is not associated with cognitive gains (Etnier, Nowell, Landers, & Sibley, 2006; Angevaren et al., 2008). The ability to enhance neurocognition has gained importance as recent studies have provided evidence that neurocognitive dysfunction predicts incident cognitive impairment (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001), dementia (Andel et al., 2008), and mortality (Bassuk, Wypij, & Berkman, 2000; Fried et al., 1998; Kuh, Richards, Hardy, Butterworth, & Wadsworth, 2004; Smits, Deeg, Kriegsman, & Schmand, 1999; Whalley & Deary, 2001), independent of traditional risk factors (Pavlik et al., 2003), indicating that cognitive status may provide a non-invasive index of neurobehavioral risk.

As discussed in previous reviews (van Uffelen, Chin, Hopman-Rock, & van, 2008b), elucidating the relationship between enhanced physical status and cognition is problematic due the current state of the literature, which has been limited by frequent use of cross-sectional study designs, inconsistencies in the assessment of aerobic fitness, variability in selection of neuropsychological tests, and heterogeneous control groups within RCTs (Etnier et al., 2006; Angevaren et al., 2008). This problem is further confused by two recent meta-analyses demonstrating that improved aerobic fitness does not consistently improve cognitive performance across RCTs (Etnier et al., 2006; Angevaren et al., 2008). Despite the discrepant findings among RCTs, observational

studies have generally reported a positive relationship between physical activity, cardiovascular fitness, and greater neurocognitive performance.

1.6.1.1 Exercise and Neurocognition: Observational Studies

Multiple cross-sectional studies have demonstrated that physical activity is associated with improved cognitive function. Spirduso (Spirduso, 1975; Spirduso & Clifford, 1978; Spirduso, 1980) was the first to investigate this relationship, demonstrating that physically active older adults exhibit faster reaction time in comparison with their sedentary counterparts, a finding that spurred scientific interest in the role of physical activity in slowing the aging process. Epidemiological studies have generally supported these initial cross-sectional findings, demonstrating that more physically fit and more physically active individuals tend to exhibit better cognitive function relative to their sedentary counterparts.

In a sample of approximately 14,000 middle-aged adults from the Atherosclerosis Risk in Communities Study, Cerhan and colleagues (Cerhan et al., 1998) reported a positive association between neuropsychological performance and forced expiratory volume (FEV₁), an index of cardiorespiratory fitness. Specifically, higher FEV₁ was associated with better performance on the Digit Symbol Substitution Test, Word Fluency, and Delayed Word Recall. Binder and colleagues (Binder, Storandt, & Birge, 1999) reported similar results in a sample of 125 men and women aged 75 and older, noting a positive association between neuropsychological performance and Physical

Performance Test measures. This relationship was strongest for tests with a strong psychomotor speed component and was not significantly attenuated after controlling various indices of intelligence, indicating that this effect may be specific to tasks involving psychomotor speed, independent of general cognitive abilities. More recently, Hillman and colleagues (Hillman et al., 2006) demonstrated that higher levels of physical activity behavior were associated with a quicker reaction time among community-dwelling volunteers. In their study, complex reaction time was used as an index of executive function due to the strong interference component of this test, which requires participants to simultaneously respond to task-relevant stimuli while ignoring task-irrelevant stimuli. In addition to finding an association between higher levels of cardiovascular fitness and better cognitive performance, the authors found that fitness was more strongly associated with performance on tasks requiring greater amounts of response inhibition and complex attentional processes.

Recent studies have examined the effects of exercise training characteristics as predictors of improved cognitive function, including the intensity of exercise and duration or amount of time spent exercising. In a recent cross-sectional examination of 1,927 healthy adults aged 45-70, Angevaren and colleagues (Angevaren et al., 2007) found that greater intensity of physical activity, but not duration, was associated with improved cognitive performance. Physical activity was indexed using a self-report measure in which participants were asked about the frequency and duration of their

participation in various leisure activities (e.g. walking, bicycling, housekeeping, gardening, etc.). All activities were then coded and given a specific metabolic equivalent (MET) value. Greater intensity of reported physical activity were associated with better processing speed, memory, mental flexibility, and overall cognitive function, but were not associated with the amount of time spent in various physical activities.

Furthermore, these associations were not attenuated by controlling for cardiovascular risk factors, such as BP, glucose, total and high density cholesterol, body mass index, and smoking status. In an study investigating predictors of cognitive decline among 1,192 community-based volunteers, Albert and colleagues (Albert et al., 1995) examined a similar question utilizing structural equation modeling (SEM). They found that greater levels of objectively measured aerobic fitness, indexed by peak expiratory flow rate, was the best predictor of cognitive function second only to level of education. The authors also found a direct association between strenuous levels of activity and change in cognitive performance, as well as an indirect association mediated by peak expiratory flow rate. However, moderate rates of physical activity were not significantly associated with cognitive change, suggesting a possible threshold effect of the influence of physical activity on cognitive function. Despite these positive findings, the majority of extant studies have focused on the total amount or duration of physical activity as predicting cognitive function (Weuve et al., 2004). Singh-Manoux and colleagues (Singh-Manoux, Hillsdon, Brunner, & Marmot, 2005a), for example, found that higher levels of physical

activity were associated with better cognitive performance in prospective analyses of middle-aged adults from the Whitehall II Prospective Cohort Study. Notably, a dose-response relationship was observed between higher levels of physical activity and improved levels of fluid intelligence. Individuals reporting persistently low levels of physical activity were at particularly elevated risk for cognitive decline over the course of the study.

Although cross-sectional studies have generally found support for the association between greater physical fitness and enhanced cognitive function, cross-sectional study designs cannot provide causative inference. The fitness and cognition relationship is potentially confounded by a number of factors, such as differences in nutrition, educational factors, or personality characteristics. It is also possible that exercise may confer greater cognitive gains only after years of repeated behavior, such that cross-sectional studies assessing exercise and cognition at any one time-point may not reflect the cumulative effect of physical activity due to variation in the assessment of fitness indices. Longitudinal studies provide greater insight into the changes in cognitive function associated with physical activity over sustained periods of time.

Multiple prospective studies have examined the protective effect of physical activity on cognitive functioning (Barnes, Whitmer, & Yaffe, 2007; Scarmeas & Stern, 2003) and have generally supported the positive relationship demonstrated in cross-sectional studies, demonstrating that sustained levels of aerobic exercise may be

associated with improved cognitive reserve (Dik, Deeg, Visser, & Jonker, 2003), processing speed (Richards, Hardy, & Wadsworth, 2003), and memory (Laurin et al., 2001; Broe et al., 1998). Moreover, regular physical activity confers a decreased risk of cognitive impairment (Scarmeas, Levy, Tang, Manly, & Stern, 2001) and dementia (Singh-Manoux et al., 2005a). Prospective studies have generally explored the total amount of time spent exercising, or exercise habits, as predictors of neurocognition, largely ignoring the effects of exercise intensity. Sturman and colleagues (Sturman et al., 2005) investigated the relationship between physical activity and cognitive decline in a sample of 4,055 community-dwelling individuals, finding that each additional hour of physical activity per week was associated with a slower rate of cognitive decline, in a dose-response fashion. However, these effects were attenuated after controlling for participation in cognitive activities, depression, and vascular disease. This effect was also attenuated when individuals with compromised cognitive function at baseline (i.e. whose global cognitive score \leq 10th percentile) were excluded, indicating that the effects of physical activity may have been more beneficial among those with lower cognitive performance. Yaffe and colleagues (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001) reported similar findings, noting that self-reported walking was associated with decreased risk of cognitive decline among 5,925 older women. Similarly, Weuve and colleagues (Weuve et al., 2004) found that total energy expenditure was associated with less cognitive decline in a sample of approximately 19,000 women from the Nurses'

health study. Stewart and colleagues (Stewart, Prince, & Mann, 2003) also reported an association between vigorous exercise and a reduced risk of cognitive decline, noting that this association was particularly strong among individuals 75 years and older.

These findings have been extended to study the effects of physical activity as a means of protecting older adults against dementia in later life. Rovio and colleagues (Rovio et al., 2005) recently examined this relationship in 1449 older adults, finding that higher levels of leisure-time physical activity were associated with 52% and 62% reduced risk of developing dementia and AD, respectively. Moreover, this effect was independent of age, education, APOE genotype, vascular co-morbidities, and smoking habits. Larson and colleagues (Larson et al., 2006) reported similar findings in a sample of 1740 individuals 65 years of age or older. At baseline, data on exercise habits, cardiovascular risk factors, cognitive function, and background characteristics were collected, after which participants were followed for approximately 6 years. Participants who reported exercising three times per week or more demonstrated a 38% reduced risk for the development of dementia during the follow-up period compared to those reportedly exercising less than three times per week. Laurin and colleagues (Laurin et al., 2001) examined this relationship in a sample of 9,008 randomly selected community volunteers, aged 65 years and older. Physical activity was associated with a reduced risk of cognitive impairment (42%), AD (50%), and dementia of any type (37%) over the course of their 5-year follow-up. Most recently, Andel and colleagues (Andel et al.,

2008) reported that regular physical exercise was associated with reduced risk of dementia in a sample of 2,870 individuals from the Swedish Twin Registry. Notably, this study was strengthened by incorporating a substantially longer follow-up period of 31 years. The authors found that 'light' exercise (i.e. low frequency) was associated with a 37% reduced risk of dementia, whereas more 'regular' exercise reduced the risk of dementia by 66%. When analyses were limited to co-twin control analyses, the relationship between exercise and dementia was similar with a 50% reduced risk associated with exercise, but did not reach statistical significance, possibly due to the vastly limited sample size of this subset analysis.

Although training features such as intensity and duration reflect variations in the characteristics of exercise training, they do not provide an accurate measure of changes in cardiovascular fitness. Objective measures of fitness provide a more accurate index of the impact of exercise on cardiovascular health. Colcombe and colleagues (Colcombe et al., 2004) reported similar findings in a sample of 41 community-dwelling older adults. Estimated fitness level was derived from was indexed using an index of peak VO_2 derived from the Rockport 1-mile test. Participants were then asked to perform a controlled reaction time test while undergoing functional brain imaging. Correct reaction time responses were associated with greater activation in the medial frontal gyrus, superior frontal gyrus, and superior parietal lobe, and were associated with decreased activity in the anterior cingulate gyrus. Furthermore, these results were not

significantly attenuated following post-hoc adjustment for regional gray matter volume, indicating that this effect was specific to the white matter integrity of these regions. Combined results showed a non-significant linear trend between higher VO_{2max} levels and greater cognitive performance.

Several studies have examined the longitudinal association between cognition and objective measures of fitness, reducing the influence of self-report biases. Although self-reported physical activity practices are associated with physical fitness, objective measures provide a more accurate index of cardiovascular health and reduce self-report bias. Barnes and colleagues (Barnes et al., 2003) investigated the relationship between cardiorespiratory fitness and cognitive function in a sample of 349 individuals without evidence of cardiovascular disease, musculoskeletal disability, or cognitive impairment. In the course of their six year follow-up, those participants with poorer peak VO_2 performance at baseline showed a more rapid cognitive decline. Furthermore, after adjusting for demographic and health-related covariates, peak VO_2 showed the strongest association with global measures of cognitive function and attention/executive functions. Similar findings have been reported for memory performance and self-reported physical activity in leisure time (Richards et al., 2003).

In addition to the positive findings demonstrated among healthy, older adults, several studies have replicated this relationship in clinical populations. Etnier and colleagues (Etnier et al., 1999) examined the association between cognitive function and

several indices of aerobic capacity in a sample of 98 older adults with chronic obstructive pulmonary disease (COPD). Specifically, the authors investigated whether measures of fluid intelligence, processing speed and working memory, or processing speed and inhibition were associated with differential aerobic capacities, indexed by the 6-min walk test, peak VO_2 , and FEV_1 . Across cognitive domains, greater 6-min walk distance was associated with better cognitive performance, although other fitness indices did not appear to be associated with differential cognitive performance. Etnier & Berry (Etnier & Berry, 2001) reported similar findings in an 18-month longitudinal study of COPD patients, in which decreased cardiorespiratory ventilation capacity (V_E) measured during the peak VO_2 from a treadmill test was predictive of fluid intelligence. Not all studies examining this relationship among COPD patients have reported similar findings, however (Emery, Shermer, Hauck, Hsiao, & MacIntyre, 2003).

Although greater aerobic fitness appears to be associated with better cognitive performance among individuals with COPD, this relationship is less clear among individuals with multiple sclerosis (MS). MS is a common neurological disease typified by diffuse white matter damage which primarily afflicts middle-aged and younger adults, resulting in decreased neuronal conduction capacity. Prakash and colleagues (Prakash et al., 2007) recently examined the association between peak VO_2 , cognitive performance, and functional brain activation in a sample of 24 individuals with MS, assessing a range of cognitive functions including memory, psychomotor sequencing,

verbal fluency, and executive function. In addition, participants underwent functional brain imaging while completing the Paced Visual Serial Addition Test (PVSAT). During the PVSAT, participants exhibited increased activation in the inferior and medial frontal gyri, and the level of activation in this area correlated significantly with higher levels of aerobic fitness. Furthermore, participants with better aerobic fitness showed decreased activation in the anterior cingulate gyrus during periods of increased frontal activity. However, none of the other 7 cognitive tests were associated with aerobic fitness in this study.

Finally, recent studies have examined whether individual differences may moderate the effects of exercise on cognitive performance. Several studies have examined whether physical activity may confer additional benefits among individuals carrying the APOE ϵ 4 allele, which is associated with an increased risk of dementia and AD (Blair et al., 2005; Scarmeas et al., 2004; Podewils et al., 2005). Podewils and colleagues (Podewils et al., 2005) examined this association among 3,375 older men and women, investigating the association between leisure-time energy expenditure and the development of cognitive disorders over a 4.5 year follow-up. Individuals in the highest quartile of energy expenditure demonstrated a 15% reduced risk of incident dementia compared with individuals in the lowest quartile. Furthermore, individuals engaging in > 4 leisure activities on a regular basis demonstrated a 39% decreased relative risk of

dementia, as well as reduced risk for AD and VaD. Notably, examination of APOE genotype showed that $\epsilon 4$ carriers experienced the greatest benefit with exercise, whereas a non-significant association was evident in non-carriers.

Despite these positive findings, several notable negative findings deserve further mention. In a meta-analysis examining the relationship between cardiovascular health and neurocognition, Etnier and colleagues (Etnier et al., 2006) found no association between greater aerobic fitness and enhanced cognitive function when data from eight separate cross-sectional studies were combined, including 27 effect sizes representing data from 214 subjects. Several prospective studies have also failed to demonstrate a protective effect of physical activity on cognitive function. In a prospective examination of 6,158 individuals aged 65 or older, Wilson and colleagues (Wilson et al., 2002) found that weekly hours of reported physical activity did not protect against the development of AD, but that cognitive activity (i.e. leisure-time reading) was associated with a 64% reduction in the incidence of AD during a 4-year follow-up assessment. Yamada and colleagues (Yamada et al., 2003a) reported similar findings in a longitudinal cohort study of 1,774 Japanese adults, finding that physical activity levels were not associated with an reduced risk of AD or VaD. In addition, the only study to examine physical activity as a protective factor against the development of Parkinson's Disease (PD) reported negative findings (Logroscino, Sesso, Paffenbarger, Jr., & Lee, 2006)

demonstrating that neither total energy expenditure nor total time spent walking protected against the development of PD. Finally, studies examining individual differences based on genotype have also reported discrepancies. Two large-scale prospective trials reporting that regular exercise protects against the development of AD did not find evidence that this relationship was moderated by APOE genotype (Lindsay et al., 2002; Schuit, Feskens, Launer, & Kromhout, 2001). Nevertheless, the vast majority of extant data indicate that greater physical activity and cardiovascular fitness are associated with better neurocognitive function.

As demonstrated above, longitudinal studies have generally demonstrated a relationship between physical activity and enhanced cognitive function. Discrepant findings are not uncommon, however, and the majority of those studies examining other leisure-time activities have demonstrated that these are also associated with improved cognition, in some cases mediating the physical activity and cognition relation. RCTs, therefore, offer the best experimental design for assessing the relationship between physical activity and neurocognition in a controlled setting.

1.6.1.2 Exercise and Neurocognition: Interventions

Multiple randomized and quasi-randomized trials have examined the effects of aerobic exercise on cognitive endpoints. Quasi- and non-randomized interventions have generally reported positive effects of exercise on neurocognitive performance. Although less methodologically rigorous than RCTs, these studies provide useful information on

changes in objective fitness indices and associated cognitive changes among a variety of participant populations.

In their seminal work, Dustman and colleagues (Dustman et al., 1984) conducted a 12-week trial consisting primarily of jogging / running, among 40 sedentary adults. Exercise participants demonstrated improvements on tasks associated with complex sequencing compared with controls subjects, although complex reaction time was unchanged in either group. Although this study used alternating treatment assignment, it nevertheless generated interest in the use of randomized trials to investigate the aerobic fitness and cognition relationship.

Despite the systemic cardiovascular benefits of aerobic exercise, few studies have examined the cognitive effects of exercise among cardiac patients. Gunstad and colleagues (Gunstad et al., 2005) examined changes in psychomotor sequencing and executive function among 18 cardiac patients participating in a structured cardiac rehabilitation program. Participants were administered several tests of psychomotor sequencing, such as Trail Making Test A and WAIS Digit Symbol Substitution, as well as the Animal Naming Test. Following the 12-week rehabilitation program, participants experienced improvements on Trail Making A and the WAIS Digit Symbol Substitution, both tasks of psychomotor sequencing. In addition, exercisers exhibited improved cardiovascular fitness as indexed by peak METs and these gains were associated with improvements in psychomotor sequencing and, to a lesser extent, improved executive

function performance. In addition, Tanne and colleagues (Tanne et al., 2005) conducted an important trial among 25 individuals with congestive heart failure to address this question. Control patients were those that could not participate in the exercise program due to lack of medical insurance and/or because they lived too far from the exercise facility, introducing a possible source of selection bias. Participants completed neuropsychological assessments, a test of cerebral vasomotor reactivity to hypercapnia, and exercise capacity assessments before and after the intervention. Following the 18-week trial, exercisers showed improvements in tasks associated with simple and complex psychomotor sequencing. These changes were not associated with vasomotor reactivity, however, which did not improve despite improved exercise capacity, possibly indicating that improved cardiovascular fitness does not improve cerebrovascular oxygenation efficiency.

Randomized control trials (RCTs) have been used to reduce the selection bias that has confounded the findings of observational studies. Exercise training trials have generally ranged in duration from 2 months to one year, with the majority of studies utilizing 3-month treatment paradigms. RCTs have varied substantially in the frequency of exercise training, with some requiring participants to meet once per week and others daily. RCTs have generally utilized aerobic exercise paradigms, such as running (Kramer et al., 1999), walking (Hawkins, Kramer, & Capaldi, 1992b), and swimming (Moul, Goldman, & Warren, 1995), although several have investigated the

ability of progressive resistance training as an adjunctive treatment. Although neurocognitive data has been examined in each study, this was a secondary endpoint in many RCTs, with a primary goal of improving depression (Khatri et al., 2001; Hoffman et al., 2008b), cardiovascular health (Barry et al., 1966), or behavioral outcomes, such as reduced falls among elderly patients (Rikli & Edwards, 1991).

Multiple trials have been conducted among both healthy (Angevaren et al., 2008) and clinical populations, including individuals with COPD (Emery, Schein, Hauck, & MacIntyre, 1998b), multiple sclerosis (Oken et al., 2004), major depression, MCI (Scherder et al., 2005), and AD (Friedman & Tappen, 1991). Among healthy individuals, trials have generally been performed among sedentary middle-aged and older adults (Palmer, 1995), although trials among elderly adults have also been conducted (McMurdo & Rennie, 1994). Although many have recruited volunteers from community-based samples (Williams & Lord, 1997b), others have recruited from long-term care facilities (Cott, Dawson, Sidani, & Wells, 2002). Aerobic training interventions have typically relied on treatment paradigms derived from the cardiac rehabilitation literature (Barry, Steinmetz, Page, & Rodahl, 1966), consisting of 12-16 weeks of aerobic exercise (Blumenthal et al., 1991) with few studies utilizing more extensive follow-up periods (Oken et al., 2006). Control conditions vary widely between trials with most using wait list control conditions (Blumenthal et al., 1991), although stretching, toning or yoga (Fabre, Chamari, Mucci, Masse-Biron, & Prefaut, 2002), education or cognitive

activities (Blumenthal et al., 1999), and anti-depressant medication (Blumenthal et al., 1999) conditions have also been used.

Aerobic exercise interventions have been utilized in both healthy and clinical adult populations. Although intervention formats and design characteristics have been applied similarly between healthy and clinical populations the mechanisms by which aerobic exercise might improve cognition are somewhat different between the two. For example, improved cognitive performance among individuals with progressive degenerative disorders, such as AD (Powell, 1974) or MCI (Scherder et al., 2005), may result from somewhat distinct processes as compared with otherwise healthy, sedentary adults.

Among non-clinical populations, the effects of exercise have been most extensively examined among sedentary and/or elderly adults. Results have varied widely between studies, underscoring the need to investigate mediators of cognitive improvement. Blumenthal and colleagues (Blumenthal et al., 1989) examined the effects of a 4-month exercise intervention among sedentary, middle-aged adults. Although physiological function was significantly improved during the study, as indexed by improved peak VO_2 , as well as reduced lipids, weight, and BP, no changes in cognitive function were observed across tests from an extensive neuropsychological battery, heavily weighted with tasks of processing speed and executive function. In a closer examination of reaction time measures from the same sample, Madden and colleagues

(Madden, Blumenthal, Allen, & Emery, 1989) noted that reaction time did not improve in exercisers, despite improved aerobic capacity. In a study combining results from young and older subjects, Hassmen and colleagues (Hassmen, Ceci, & Backman, 1992) found that structured walking improved aerobic capacity as well as performance on the digit span test. Interestingly, reaction time was unchanged despite the increase observed in aerobic health.

Studies examining the effects of exercise among older populations have generally reported positive findings (Hassmen et al., 1992; Hawkins, Kramer, & Capaldi, 1992a; Fabre et al., 2002). Fabre and colleagues (Fabre et al., 2002) found that a two-month walking / running intervention improved memory among exercisers relative to controls. Interestingly, this study also incorporated a combined exercise and mental training group, which showed substantial improvements above all other groups. Kramer and colleagues (Kramer et al., 2001) reported similar findings, showing moderate improvements in working memory and executive function among exercisers following a 6-month brisk walking intervention among sedentary middle-aged adults. Similarly, Williams & Lord (Williams & Lord, 1997a) found that a 12-month group exercise program was associated with improved reaction time among 187 community-dwelling women. Discrepant findings have also been reported, however. Emery and colleagues (Emery & Gatz, 1990) found that a 12-week exercise intervention did not improve cognitive performance in any domain among 48 older men and women.

Aerobic exercise has been examined as a potential treatment for multiple cognitive end-points among wide-ranging clinical populations. Cognitive disorders of later life such as AD (Cott et al., 2002) and MCI (Scherder et al., 2005) have been examined, as well as cognitively compromised nursing home residents (Cott et al., 2002). Extending work from the cardiac rehabilitation literature, several investigators have conducted aerobic trials among specific health populations such as chronic obstructive pulmonary disease (COPD) (Emery, Schein, Hauck, & MacIntyre, 1998a), multiple sclerosis (Oken et al., 2004), and major depressive disorder (MDD) (Khatri et al., 2001; Hoffman et al., 2008a).

Most relevant to the current examination, Pierce and colleagues (Pierce, Madden, Siegel, & Blumenthal, 1993) examined the effects of a 16-week aerobic exercise intervention on cognitive function among 90 patient with mild HTN. Participants completed tests of processing speed, executive function, working memory, and memory for both figural and narrative material. Despite the number and breadth of testing performed, no significant differences were noted between exercisers and control participants.

Six previous meta-analyses have investigated the effects of aerobic exercise interventions on cognitive function. Etnier and colleagues (Etnier et al., 2006) examined the effect of acute and long-term exercise on cognition, combining nearly 200 studies and 134 effect sizes among participants aged 6 to 90 years. Exercise was associated with

small improvements cognitive performance ($ES = .25$) and this effect appeared to be strongest among middle-aged adults (aged 45-60). Interestingly, results were found to vary by methodological quality, with higher quality studies finding no effects of treatment on cognitive performance.

More recently, Etnier and colleagues (Etnier et al., 2006) conducted meta-regression analyses to examine whether changes in aerobic fitness were associated with corresponding changes in cognitive performance. Among RCTs, twenty-four studies were examined, yielding 78 effect sizes from 934 participants. Changes in fitness were not associated with changes in cognitive function, and this effect did not differ significantly between studies or by moderating factors.

Colcombe and Kramer (Colcombe et al., 2003a) conducted a meta-analytic study of RCTs investigating the effects of aerobic exercise training on cognition. Eighteen studies and 197 effect sizes were included in the analyses. Aerobic exercise trials were associated with improved cognitive performance in executive processes, controlled processes, spatial performance, and speed tasks. Furthermore, aerobic training trials that combined strength training were associated with greater improvements compared to aerobic training alone and trials among participants aged 66-70 appeared to show the greatest improvements. Methodological variation between trials was not considered in these analyses.

Heyn and colleagues (Heyn et al., 2004) examined the effects of randomized

trials evaluating the effects of exercise in persons 65 years of age or older with cognitive impairment. Specifically, the effects of exercise was investigated on multiple outcomes, including strength, physical fitness, functional performance, cognitive performance, and behavior. Thirty studies were included in the analyses, incorporating data from 2020 participants, although only 12 effect sizes from 10 studies were available for cognitive outcomes. When analyses were limited to studies examining Exercise was associated with moderate improvement in cognitive function (ES = .57).

In the most rigorous meta-analytic study to date, Angevaren and colleagues (Angevaren et al., 2008) examined the effects of aerobic exercise trials on cognitive function among adults 55 years of age or older without cognitive impairment. Similar to Etnier and colleagues (Etnier et al., 2006) analyses, improvements in aerobic fitness were examined as a potential moderating effect. In contrast to the graded relationship between improved fitness and cognition used in the Etnier and colleagues study (Cotman & Berchtold, 2002; Cotman & Engesser-Cesar, 2002; Cotman, Berchtold, & Christie, 2007), trials were distinguished based on whether aerobic capacity was significantly improved (e.g. > 14% improvement in peak VO₂). In contrast to previous reviews, older individuals with known (e.g. AD or MCI) or suspected (e.g. depression) cognitive impairment were excluded, although clinical populations were included in the analyses (e.g. COPD). The largest changes in cognitive function were observed in motor function and auditory attention, whereas moderate improvements were observed in

cognitive speed and visual attention. However, the majority of comparisons yielded non-significant results and the authors concluded that there is insufficient evidence to show that improvements in cognitive function can be attributed to physical exercise.

We (Smith et al., 2009) recently conducted a meta-analytic synthesis of all RCTs examining the effects of aerobic exercise on cognitive performance in non-demented adults, some of whom were at risk for dementia (i.e. MCI). We found that aerobic exercise interventions were associated with modest improvements in attention / processing speed, executive function, and memory. In addition, sensitivity analyses revealed several important moderators of treatment effects. Trials of longer duration were associated with dose-response improvements in attention / processing speed. Notably, trials among individuals with MCI demonstrated greater improvement in memory performance relative to non-compromised samples, indicating that the beneficial effects of exercise on various cognitive functions may be most evident in compromised populations.

1.7 Summary of Introduction

HBP is associated with poorer cognitive function across multiple domains of function and significantly increases the risk of dementia in later life. In addition, HBP is a risk factor amenable to multiple modalities of treatment, including pharmacologic treatment, and lifestyle modification, with changes in diet and exercise. Pharmacologic treatment is an effective means of reducing blood pressure, but may result in cognitive

deficits in a number of different cognitive domains. In contrast, dietary modification and exercise have both been found to improve cognitive function, although their effects vary widely between studies. To our knowledge, no studies have examined the effects of a combined intervention of diet and exercise on cognitive function among hypertensive patients, despite the elevated risk for cognitive deficits and dementia in this group.

1.8 Aims and Hypotheses

The purpose of the present study is to examine changes in cognitive performance associated with diet and weight management in patients with HBP. Specifically, we hypothesized that (1) patients receiving exercise and DASH diet or DASH diet alone will exhibit greater improvements in cognitive function relative to controls, (2) the effects of the intervention will be moderated by baseline cardiovascular risk status, such that participants with greater levels of cardiovascular risk will exhibit greater improvements, and (3) improvements in neurocognition will be mediated by improvements in aerobic function (indexed by improved peak VO₂) and reductions in SBP. The data presented were collected as part of a larger clinical trial (the ENCORE study) (Hinderliter, 2009c), which examined the effects of weight loss and the DASH diet on blood pressure and other measures of cardiovascular health among individuals with high normal blood pressure.

2. Materials and Methods

2.1 Participants

One hundred forty four adults with high normal blood pressure were recruited for participation a larger trial examining the effects dietary modification and weight management on BP, cardiorespiratory fitness, and autonomic function, known as the ENCORE study (Hinderliter, 2009a). The current analyses were conducted among a subset of participants who had pretreatment neurocognitive data (n = 124).

2.2 Neurocognition

All participants underwent a standard neuropsychological test battery in order to assess performance in multiple domains of cognitive functioning. Tests were selected based on the brevity of their administration, availability of normative data, and the availability of multiple forms for repeat testing. The following instruments were administered individually by a trained research assistant:

2.2.1 Controlled oral word association test

The Controlled Oral Association Test (COWAT) (Wechsler D., 1956) requires participants to generate as many words as possible beginning with different letters of the alphabet in a period of one minute. The letters C, F, L and P, R, W were used in the current study. The COWAT is designed to assess verbal fluency and executive function.

2.2.2 Digit Symbol Substitution Test.

The Digit Symbol Substitution Test (DSST) (Wechsler, 1997) is a measure of executive functioning and attention from the Wechsler Adult Intelligence Scale – Revised in which participants are asked to draw symbols that match one of 10 digits copied from a key. Scores on this task are the number of correct symbols drawn in a 90-second time period.

2.2.3 Ruff 2 & 7 Test.

The Ruff 2 and 7 Test (Ruff R.M., Niemann, & Allen, 1992) is a paper-and-pencil test of vigilance / attention. Participants are required to cross out all instances of the numbers '2' and '7' under two conditions: one in which they are embedded among other digits and in the second in which they are embedded among letters. Stimuli are presented in consecutive blocks of three lines (each line consisting of 10 targets and 40 distracters) representing each condition with a 15-second time limit per block, in pseudorandom order. The score is the total number of correct cancellations within a five-minute time period.

2.2.4 Verbal Paired Associates

The Verbal Paired Associated Test (Wechsler, 1987) assesses working memory / attention by presenting participants with a list of eight word pairs, half of which were highly associated (e.g., baby-cries) and half which had a low association (e.g., school-grocery). After the list has been read aloud, participants are presented with one word from each pair and are asked to name corresponding word from the original list. The

list of words is then repeated on two subsequent trials and the recall process is repeated.

2.2.5 Digit Span

The Digit Span Test (DST) (Wechsler D., 1956) assesses attention / working memory. In this test, participants are asked to recall a list of consecutive numbers that become sequentially longer as the participants answer more trials correctly. On the first trial, participants are asked to recall the numbers in the same order in which they were presented. In the second trial, participants are asked to recall the numbers in the reverse order from which they were presented.

2.2.6 Stroop Test

The standardized version of the Stroop test used in the current study consists of three sections: word, color, and color-word (Stroop, 1935). In each section, participants are presented with a page consisting of 5 columns, each with 20 items for a total of 100 items per page. Within each section, the score is the total number of words read aloud in 45 seconds. The word section requires participants to read a list of color words ("RED", "BLUE", and "GREEN") as quickly as possible. For the color section, participants name aloud the color of a series of colored bars printed on the page. The color-word list is similar to the color list in that the task is to name the color in which each item is printed. The items in this list, however, are color names, in which the names of the items differ from the colors in which they are printed (e.g., the word *RED* is printed in blue ink). The word and color tests are believed to measure processing speed, whereas

the color-word section (also known as the 'interference' section) is believed to measure selective attention, a component of executive functioning. The Stroop Interference score was used in the present analyses, as this provides an index of controlled processing ability independent of the influence of psychomotor speed.

2.2.7 Animal Word Fluency Test

The Animal Fluency Test (VFT) (Lezak, 1995) is a test of executive function in which the participant is instructed to generate words from a specified category (in this case, animals). The score is the total number of animals generated in a 60-second time period.

2.2.1 Trail Making Test

Trail Making Test part A (Reitan, 1979) requires participants to draw consecutive lines between the numbers 1 through 25 as fast as possible. The score is the time, in seconds, required for completion and is believed to measure processing speed and selective attention. Trail Making Test Part B (Blumenthal et al., 1988b) requires participants to draw consecutive lines alternating back and forth between the numbers 1 and 13 and the letters A through L. The score is the time, in seconds, required for completion and is believed to measure visual search and attentional processes associated with executive functioning. In the present analyses, the time to complete part B minus the time to complete part A was used, providing an index of complex attentional processes.

2.3 Cardiovascular Health

All participants underwent assessments of cardiovascular health at baseline and again following the four month intervention.

2.3.1 Peak Oxygen Consumption

Maximal exercise testing was performed using the Duke-Wake Forest protocol in which graded exercise began at 3.2 kilometers per hour and 0% grade and workload was increased at a rate of 1 metabolic equivalent per minute (oxygen, 3.5 mL/kg per minute). Expired gases were collected for the determination of peak oxygen consumption using a metabolic cart (model 2900; Sensormedics, Yorba Linda, Calif). Assessments were made at baseline and again following treatment.

2.3.2 Clinic Blood Pressure

Blood pressure measurements were obtained by a trained technician with a random zero sphygmomanometer and were standardized for cuff size and position. Measurements were made on 4 separate visits during a 3-week period. At each visit, BP was measured in the nondominant arm in the sitting position 4 successive times at 2-minute intervals after an initial rest period of 5 minutes. The first BP measurement of each visit was discarded, and the average of the remaining 3 measurements represented the clinic visit BP. The overall clinic BP was then determined by averaging the mean BPs over the 4 visits. Measurements were obtained in this standardized manner at baseline and after 6 months.

2.3.3 Framingham Stroke Risk Profile

Cerebrovascular risk factor scores were determined at the baseline screening and physical examination using the Framingham Stroke Risk Profile (FSRP), a risk assessment tool used to assess the 10-year incidence of stroke (D'Agostino, Wolf, Belanger, & Kannel, 1994; D'Agostino, Sr. et al., 2008; Wolf, D'Agostino, Belanger, & Kannel, 1991). Risk factors used to assess stroke risk include SBP, diabetes mellitus, cigarette smoking, cardiovascular disease, and atrial fibrillation. Because age served as a covariate in our final analyses, they were not included in calculating FSRP scores. No participants reported a prior history of stroke.

2.3.4 Intima Media Thickness of the Carotid Arteries

Carotid artery IMT was assessed by a high-resolution B-mode ultrasound vascular imaging system (Acuson Aspen, Mountain View, CA) with a 10-Mhz linear array transducer. Ultrasound examinations of the far wall of the left and right common carotid arteries (CCAs) were used to acquire longitudinal images spanning 2 cm proximal to the carotid bulb. IMT of the far wall of the left and right CCAs was measured over a 1-cm segment using edge detection software (Carotid Analyzer 5.0.5, Medical Imaging Applications LLC, Iowa City, IA). Far wall measurements only were used as near wall measurements have been shown to have limited reliability (Appel et al., 1997).

2.3.5 Weight and Body Composition

Weight was measured by a standard balance scale. Body composition and fat distribution will be assessed by dual energy absorptiometry (DEXA). This procedure will provide measurements of fat mass, lean body mass, and percent body fat for both the whole body and designated anatomical subregions (Treuth, Hunter, & Kekes-Szabo, 1995). The DEXA scan was also used to estimate abdominal adiposity (hereafter referred to as visceral fat), which confers an increased risk of cardiovascular disease independent of obesity (Rexrode, Manson, & Hennekens, 1996).

2.4 Interventions

Participants were randomized to one of three groups: aerobic exercise and diet, diet only, or wait list control (WLC). Dietary intervention was based on the Dietary Approaches to Stop HTN (DASH) diet. All patients began with a 2-week feeding component on the Duke General Clinical Research Center (GCRC) followed by 14 weeks of eating on their own in their home environment. For the control and DASH diet only arms of the study, caloric intake was not altered, whereas the DASH and aerobic exercise arm underwent modest caloric reduction. Patients assigned to the DASH diet met with the nutritionist during their meals two times per week during the feeding component to learn the rationale for the DASH diet and receive instruction about preparing DASH food.

Participants were assigned to one of 4 caloric intakes to control their weight during the initial 2-week feeding period based on the 7-day menu cycle from the DASH

study (FAO/WHO/UNU, 1985). As with the DASH study, we based caloric intake on the World Health Organization (WHO) formula for estimating basal metabolism plus self-reported activity level (derived from the interviewer-administered Seven-Day Physical Activity Recall (PAR)), to assign participants to relevant energy levels (Blair et al., 1985).

2.4.1 DASH Diet Alone (DASH-A)

Participants in the DASH diet only condition received instruction in modifying the content of their diet to meet DASH guidelines, but were asked explicitly not to exercise or to attempt weight loss during the course of the intervention. Following the 2-week feeding period, participants received instructions on the DASH diet and feedback on their adherence to the diet in a series of small group sessions (3 to 4 participants), which were held weekly for one-half hour by a nutritionist. Participant self-monitored food intake was the basis for weekly feedback from the nutritionist regarding methods and recommendations for improving their diet. The goal of weekly sessions was to augment participants' knowledge on buying and preparing appropriate foods, to enhance their motivation to eat appropriate foods, and to overcome obstacles that might prevent them from following the diet.

The nutritionist utilized motivational interviewing strategies as a way to encourage participants to implement recommended changes in diet, which provides a method of refocusing attentional resources without engaging in unnecessary

confrontation. This approach is derived from social cognitive theory (Bandura, 1986; Watson & Tharp, 1997), as well as behavioral self-management and follows the stages-of-change (Prochaska & DiClemente, 1983) and motivational enhancement models (Bock, Marcus, Pinto, & Forsyth, 2001). Approaches are designed to enhance self-efficacy and outcome expectancies (Bandura, 1986).

2.4.2 DASH Diet Combined with Exercise and Cognitive Behavioral Weight Loss (DASH + WM)

Participants in the DASH + weight management (DASH + WM) condition received both the DASH dietary intervention as described above and participated in a program to promote weight loss consisting of 2 components: supervised aerobic exercise and Cognitive Behavior Weight Loss (CBWL).

Subjects participated in a supervised aerobic exercise program 3 times per week (on site) at a level of 70-85% of their initial heart rate reserve, which was determined at the time of the baseline treadmill test. Routine exercise was conducted under medical supervision and consisted of 10 minutes of warm up exercises, 40 minutes of biking and/or walking (and eventually jogging), and 10 minutes of cool down exercises. In order to minimize risk of musculoskeletal injury, two exercise sessions per week were augmented with 20 minutes of cycle ergometry. In the event that subjects developed knee or leg pain, more sessions on the stationary bicycle were substituted for walking and/or jogging. Subjects were instructed in how to monitor their radial pulses and

maintained their heart rates at, or above, their target heart rates for at least 30 minutes per session. A trained exercise physiologist supervised all exercise sessions and performed 2-3 random checks of heart rates per session to ensure that subjects were exercising at a sufficient intensity. In addition, the exercise physiologist obtained BP measurements during each exercise session to make sure that BP was not abnormally elevated.

In the cognitive behavior weight loss portion of the study, subjects met in small groups of 3-4 patients for instruction in weight management techniques. The program consisted of 16 weekly sessions led by a clinical psychologist certified in cognitive behavioral therapy. For patient convenience, the 30-45 minute sessions were scheduled immediately before one of the weekly exercise sessions. The primary basis for the intervention consisted of strategies taken from the LEARN program (Brownwell, 1994), an empirically supported, comprehensive behavioral weight loss program considered the state-of-the-art program for weight loss (Poston, Haddock, Dill, Thayer, & Foreyt, 2001). Lessons from the LEARN manual included strategies to modify lifestyle, attitude (i.e. cognitive restructuring), and relationships in order to improve dietary practices.

2.4.3 Usual Care Control Group

Patients in the Usual Care control group were asked to maintain their usual dietary and exercise habits for 4 months until they were re-evaluated during posttreatment assessments. Patients were contacted at monthly intervals and asked to

describe any spontaneous changes in their eating habits or food preferences, as well as completing a retrospective food recall questionnaire. Control patients were permitted to participate in the DASH diet upon completion of their 4-month posttreatment assessment, if they desired. Patients in the DASH diet alone group and Control group did not receive weight management instruction. In addition, BPs were monitored biweekly to ensure patient safety.

2.5 Data Analysis

2.5.1 Power Analysis

Following Cohen's criteria (Cohen, 1977), power was calculated to detect group differences in neuropsychological performance for a variety of effect sizes. The primary effects of interest are the treatment group differences in neurocognitive performance at 4 months, focusing on the contrasts outlined above in the analysis section. These estimates were made based on the following specifications: 1) separate general linear models for two composite neuropsychological measures; 2) pre-treatment neuropsychological performance, age, education, IMT, FSRP, and visceral fat as covariates in the model; 3) a sample size of 124 patients for analysis; 4) alpha of 0.05; and 5) an R^2 of 0.60 between the covariates and our composite measures of neuropsychological performance. By convention, 0.80 is considered to be an acceptable level of power. The proposed design will afford us adequate power to detect relatively small but clinically meaningful effects. Specifically, we will be able to detect about a

treatment difference of 0.324 standardized effect sizes in neurocognitive function to achieve 0.80 statistical power at an alpha of 0.05, or a treatment difference of 0.392 standardized effect sizes at an alpha of 0.01. If the effects turn out to be larger, power will be more than adequate to reject the null hypothesis of no treatment effect.

2.5.2 Data Reduction

In order to minimize the number of statistical tests in examining the effects of treatment on neurocognitive performance, we used principle axis factor analysis to combine information from the eight individual neuropsychological tests into two cognitive domain scores. A Scree test was used to determine the total number of factors retained for analysis. A minimum loading of .40 was required and Promax rotation was used. Based on these results we created unit-weighted composite scores by standardizing the individual neuropsychological test scores and then summing all subtests relevant to a given domain (Dana & Dawes, 2004; Wainer, 1976; Dana et al., 2004; Wainer, 1976). The final score was then scaled using the sample standard deviation, providing an index of change in neurocognitive performance in a standardized effect size (ES). These composites were then used as the criterion variable in the regression models described below.

2.5.3 Data Analysis

Separate analyses were conducted to examine 1) the effects of treatment on cognitive function, 2) moderators of treatment outcome and 3) mediators of any

observed treatment effects. General linear models were used to examine the effects of treatment within each cognitive domain. Within each model, baseline cognitive performance, age, years of education, IMT, FSRP, visceral fat, and group assignment served as predictors with posttreatment cognitive performance as the outcome variable. All participants with pretreatment neurocognitive data were included in analyses, regardless of their adherence to the study protocol. Within each model, planned contrasts were used to compare 1) the DASH + WM with controls and 2) the DASH-A group with controls. In order to examine treatment mediation, two dummy variables were created corresponding to these planned contrasts. As explained below, mediation was established if the regression coefficients for these dummy variables were substantially reduced following the inclusion of the mediating variable.

In order to examine moderators and mediators of treatment outcomes, the criteria set forth by Baron and Kenny (Baron & Kenny, 1986) were used, although other definitions have also been outlined (Collins, Graham, & Flaherty, 1998; Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). Within this framework, moderation is generally defined as the effect of a predictor depending on the level or value of a second predictor. This was assessed statistically by examination of the interaction between pretreatment characteristics and treatment group assignment. In contrast, mediation is typically defined as a variable that represents an intervening or explanatory mechanism in the causal chain between predictor and outcome. Accordingly, the statistical prerequisites

for mediation are 1) a nonzero relation between the predictor and the outcome; 2) a nonzero relation between the putative mediator and the outcome; and 3) a nonzero relation between the predictor and the mediator. The mediator is also hypothesized to be in the causal path of the relationship between the predictor and the outcome.

Mediation is then tested by entering both the mediator and predictor into a regression-type equation simultaneously. If the relation between the predictor and outcome is diminished substantially with the addition of the mediator to the model, and if the relation between the mediator and outcome remains statistically significant, the mediation hypothesis is supported.

Moderation was tested by evaluating the interaction terms between group assignment and two measures of baseline cardiovascular health: FSRP and IMT. In contrast, mediation was tested by including measures of changes in cardiovascular fitness: peak VO₂, SBP, and weight. In the present study, support for mediation would be demonstrated if the regression coefficient for group assignment was weakened after introduction of the cardiovascular fitness variable. In order to provide a statistical test for mediation, we used a Sobel test (Sobel, 1990) to assess whether each cardiovascular fitness variable was a significant mediator of the observed treatment effects. In order to reduce the heterogeneity in model residuals, standard errors were estimated using bootstrap resampling techniques, as described in detail elsewhere (Preacher & Hayes, 2008).

Model assumptions of additivity, linearity, and distribution of residuals, were evaluated and found to be adequate prior to analysis. Regression coefficients for continuous predictor variables were scaled using the interquartile range of the predictor variable. This scaling allows the predictor to maintain its continuous form, but yields a coefficient that can be interpreted as comparing a “typical” person in the middle of the upper half of the predictor distribution with a “typical” person in the middle of the lower half of the predictor distribution.

3. Results

3.1 Sample Characteristics

Participants in the current sample were recruited as part of a larger clinical trial examining the effects of weight loss and the DASH diet on BP and other cardiovascular endpoints (the ENCORE study)(Hinderliter, 2009b). Neurocognitive data from 124 of the original 144 patients (87%) were available for use in the final analysis, including 80 women (64%) and 45 men (36%). Four participants with baseline neurocognitive data were not available for retesting at posttreatment, including 3 participants who dropped out (2 from DASH + WL and 1 control) and one participant from the DASH + WL group who did not complete neurocognitive posttreatment assessments due to logistical constraints, but completed all other posttreatment assessments.

Background characteristics for the sample are presented in Table 1. The sample was generally middle-aged and largely comprised of either Caucasians (61%) or African-

Americans (38%). Participants had mildly to moderately elevated SBP and DBP (mean SBP = 138.3, SD = 8.4; mean DBP = 86.1, SD = 6.5) and were either overweight or obese (mean BMI = 32.8, SD = 3.8). No participants in the sample reported a history of stroke and only one participant was diabetic. Four participants reported a diagnosis of attention deficit hyperactivity disorder (ADHD) and 5 participants reported a history of depression.

Table 1: Background characteristics of sample. Data are given as mean (SD) unless otherwise indicated. SBP indicates systolic blood pressure; DBP indicates diastolic blood pressure; FSRP = Framingham Stroke Risk Profile; IMT = intima medial thickness; mm Hg indicates millimeters of mercury; KGS indicates kilograms.

	Treatment Group			
Variable	WM + DASH	DASH-A	Control	Cohort
Males, n (%)	27 (68)	23 (61)	27 (64)	97 (61)
Whites, n (%)	11 (28)	20 (53)	17 (42)	48 (40)
Table 1, continued				
Age, y	52.1 (10.2)	52.3 (9.5)	51.5 (9.0)	52.0 (9.5)
College Degree, n (%)	26 (39)	23 (34)	18 (27)	67 (56)
Married, n (%)	31 (72.1)	26 (68.4)	20 (46.5)	77 (62.1)
Current Smoker, n (%)	2 (4.7)	3 (7.9)	4 (9.3)	9 (7.3)
Hypertensive, n (%)	21 (48.8)	16 (42.1)	18 (41.9)	55 (44.4)

Family history of hypertension, n (%)	30 (69.8)	31 (81.6)	34 (79.1)	95 (76.6)
Clinic SBP, mm Hg	138.7 (8.1)	137.5 (8.5)	138.6 (8.7)	138.3 (8.4)
Clinic DBP, mm Hg	85.4 (7.2)	87.2 (6.4)	85.7 (5.9)	86.1 (6.5)
Weight, kg	93.9 (14.5)	93.9 (13.2)	92.8 (15.2)	93.5 (14.3)
BMI, kg / m²	32.8 (4.1)	32.8 (3.4)	32.7 (3.9)	32.8 (3.8)
Visceral Fat, %	38.3 (7.0)	36.5 (7.1)	36.5 (5.9)	37.1 (6.7)
Table 1, continued				
IMT, mm	0.68 (0.17)	0.70 (0.11)	0.71 (0.13)	0.70 (0.14)
FSRP	8.5 (2.9)	8.4 (3.1)	8.1 (2.8)	8.3 (2.9)
Peak Oxygen Consumption, mL/kg/min	23.7 (6.5)	23.5 (6.7)	23.6 (6.0)	23.6 (6.3)
Visceral Fat, %	38.3 (7.0)	36.5 (7.1)	36.5 (5.9)	37.1 (6.7)
Alcohol use, < 1 serving/wk	9 (7.3)	11 (8.9)	9 (7.3)	95 (76.6)

3.2 Neurocognitive Functioning

Neuropsychological characteristics of the study sample are presented in Table 2.

Results from the principal component factor analysis revealed two factors from the neuropsychological battery corresponding to two cognitive domains, which we have

labeled Executive Functioning (Trail Making Test B – A, Stroop interference, Verbal Paired Associates, COWAT, Animal Naming, and Digit Span) and Vigilance (Digit Symbol Substitution and Ruff 2 & 7 test). The posttreatment factor structure of neuropsychological performance was similar to baseline.

Table 2: Factor loadings with individual tests. Cognitive tests in bold indicate inclusion on the respective composite cognitive measure.

<u>Test</u>	<u>Executive Functioning</u>	<u>Vigilance</u>
<i>Pretreatment</i>		
Table 2, continued		
Trail Making Test B – A	-57	-41
Stroop Interference	48	19
Ruff 2 & 7 Test (total correct)	6	84
Digit Symbol Substitution Test	14	72
Verbal Paired Associates	55	-2
COWAT	43	55
Digit Span	61	36
Animals	72	1
<i>Posttreatment</i>		
Trail Making Test B – A	-52	-59

Stroop Interference	40	25
Ruff 2 & 7 Test (total correct)	9	86
Digit Symbol Substitution Test	23	83
Verbal Paired Associates	66	11
COWAT	75	32
Digit Span	45	54
Animals	71	12

3.3 Treatment Effects

3.3.1 Treatment Effects on Cardiovascular Health

As previously reported, results from the larger trial (ENCORE) demonstrated the the intervention successfully reduced BP, improved aerobic fitness, and improved other indices of cardiovascular health, including left ventricular wall thickness and arterial stiffness (Hinderliter, 2009d). As shown in Table 3, participants in the current study exhibited improvements in cardiovascular fitness, lower weight, and reduced BP, consistent with results of the larger trial. Specifically, participants in the DASH + WM group demonstrated marked improvements in peak VO₂ ($F_{1,99} = 51.94, P < .001$), weight ($F_{1,98} = 140.26, P < .001$), SBP ($F_{1,99} = 16.43, P < .001$), and DBP ($F_{1,98} = 9.14, P = .003$). Similarly, participants in the DASH-A group exhibited improvements in SBP ($F_{1,99} = 5.77, P = .018$) and DBP ($F_{1,99} = 4.70, P = .033$) relative to controls, although neither peak VO₂ ($F_{1,99} = 0.50, P = .482$) nor weight loss ($F_{1,98} = 140.26, P < .0001$) were not significantly

improved with treatment.

Table 3: Changes in weight, aerobic fitness, blood pressure, and neurocognition.

Variable	Time	Treatment Group†			Contrast P‡	
		DASH + WM	DASH-A	Control	DASH + WM vs Control	DASH-A vs Control
Weight, kgs	Before	93.9 (15.0)	93.9 (13.2)	93.2 (15.1)	.841	.828
	After	85.2 (13.6)	93.1 (13.6)	93.2 (15.2)	<.0001	.505
BMI, kg/m ²	Before	33.2 (4.5)	33.3 (3.9)	33.3 (4.4)	.943	.981
	After	30.0 (4.3)	32.9 (3.4)	33.2 (3.9)	<.0001	.483
Peak VO ₂ , mL/kg/min	Before	23.8 (6.6)	23.5 (6.7)	23.6 (6.0)	.884	.954
	After	29.0 (9.0)	23.1 (6.7)	22.5 (5.7)	<.0001	.482
SBP, mm Hg	Before	138.8 (8.4)	137.5 (8.5)	138.5 (8.8)	.881	.604
	After	125.1 (12.7)	127.8 (13.9)	136.1 (15.4)	<.001	.033
Table 3, continued						
DBP, mm Hg	Before	85.7 (7.2)	87.2 (6.4)	85.9 (5.9)	.907	.375
	After	77.8 (9.1)	79.5 (8.3)	82.8 (8.3)	.003	.033
Executive Function Composite	Before	0.06 (1.02)	-0.22 (1.14)	0.22 (0.89)	.739	.135
	After	0.26 (0.99)	-0.20 (1.12)	0.04 (0.90)	.014	.266
Vigilance Composite	Before	0.16 (0.89)	-0.14 (1.11)	0.12 (1.0)	.774	.206
	After	0.29 (0.92)	-0.03 (1.06)	-0.01 (1.06)	.023	.036
DSST	Before	60.2 (8.9)	54.2 (13.3)	57.4 (9.7)	.225	.184
	After	62.8 (9.7)	57.1 (12.5)	59.1 (10.8)	.599	.715
Ruff 2 & 7	Before	236.0 (53.7)	230.8 (46.1)	243.2 (50.5)	.513	.278
	After	253.0 (51.8)	247.6 (46.0)	242.2 (55.3)	.006	.021
Trail's B – A	Before	44.0 (34.7)	47.2 (37.0)	37.6 (27.8)	.372	.198
	After	35.1 (20.3)	46.1 (31.0)	40.1 (30.2)	.026	.696
VPA	Before	17.3 (3.2)	17.0 (3.9)	17.2 (4.5)	.883	.786
	After	18.8 (3.2)	17.5 (3.5)	17.8 (4.0)	.045	.541
COWAT	Before	39.1 (11.2)	37.8 (11.4)	37.8 (10.7)	.689	.932
	After	40.8 (12.9)	39.0 (9.9)	40.1 (10.6)	.986	.699
Animals	Before	21.3 (5.7)	20.5 (5.3)	21.7 (5.6)	.650	.357
	After	21.5 (5.7)	21.2 (6.0)	21.5 (4.9)	.853	.447
Stroop	Before	-1.5 (8.3)	-4.1 (7.3)	-0.3 (7.7)	.515	.031
	After	0.18 (9.2)	-3.3 (7.3)	-2.6 (8.3)	.024	.523
Digit Span	Before	15.1 (3.4)	14.8 (4.2)	15.5 (3.4)	.536	.389
	After	15.6 (3.7)	14.8 (3.7)	16.5 (3.9)	.853	.131

BMI indicates body mass index, which is calculated as weight in kilograms divided by the square of height in meters.

† Data are given as mean (SD).

‡ Contrasts for pretreatment means compare raw group means. Posttreatment values were compared after adjusting for pretreatment values, age, education, intima media thickness, Framingham Stroke Risk Profile, and abdominal adiposity.

3.3.2 Treatment Effects on Neurocognitive Functioning

Examination of *a priori* ANCOVAs demonstrated that the DASH + WM group exhibited improved executive function relative to controls ($F_{1,92} = 7.35, P = .008$), although the DASH-A group did not improve relative to controls ($F_{1,92} = 1.57, P = .214$) (Table 3) (Figure 1). Specifically, the DASH + WM group exhibited improvement in Executive Function (mean ES = 0.21, 95% CI = 0.03, 0.39), whereas the DASH-A group's performance remained unchanged (mean ES = 0.02, 95% CI = -0.15, 0.19) and did not differ from the control group (mean ES = -0.14, 95% CI = -0.31, 0.04). In addition to group assignment, higher baseline executive function, older age, greater FSRP levels, and elevated levels of visceral fat were predictive of posttreatment executive function (Table 4).

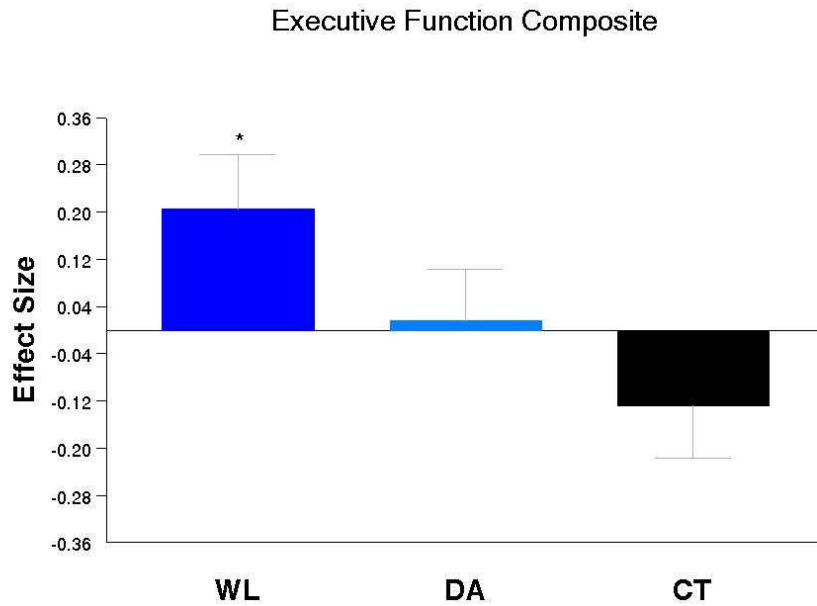


Figure 1: Posttreatment Executive Function performance adjusted for age, education, IMT, FSRP, visceral fat, and pretreatment performance. WL = DASH + WM group, DA = DASH-A group, CT = control group. * = significant at $p < .05$.

Table 4: Effects of treatment and model covariates on executive function. FSRP = Framingham Stroke Risk Profile; IMT = intima medial thickness. Regression coefficients are scaled by the interquartile range of the predictor variable. Regression coefficients can thus be interpreted as comparing a typical person in the middle of the upper half of the predictor distribution with a typical person in the middle of the lower half of the predictor distribution. † = $p \leq .10$; * = $p \leq .05$; ** = $p \leq .01$.

Predictor	Interquartile Range	Regression coefficients
Baseline executive function	1.24	0.95**
Age, yrs	14.5	-0.19*
Education, yrs	4	0.15†
IMT, mm	0.16	-0.06
FSRP	2	0.11*
Visceral fat, %	10.1	-0.20*
DASH + WM vs. Control	1	0.35**
DASH-A vs. Control	1	0.15

Examination of changes in individual neurocognitive measures (Figure 2) demonstrated that the DASH + WM group exhibited improvements in Trail Making Test ($F_{1,95} = 5.46, P = .022$), Verbal Paired Associates ($F_{1,94} = 4.35, P = .040$), and the Stroop Interference Test ($F_{1,93} = 5.96, P = .017$). Performance on the COWAT ($F_{1,95} = 0.00, P = .982$), animal naming ($F_{1,94} = 0.02, P = .894$), and digit span ($F_{1,95} = 0.02, P = .883$) were not improved with treatment relative to controls.

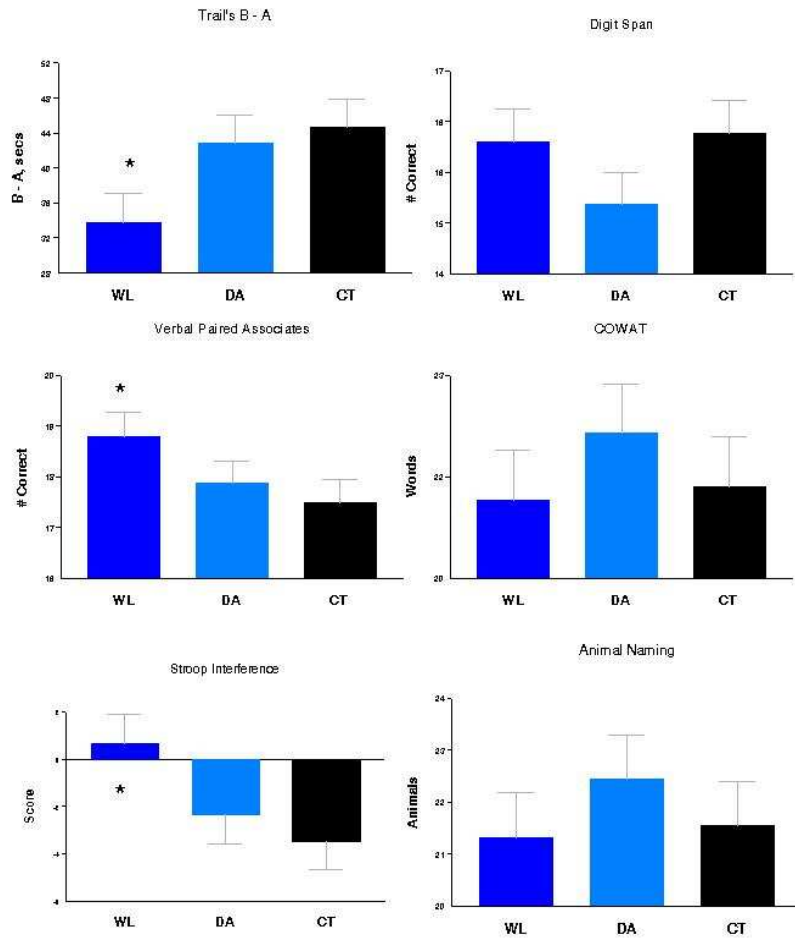


Figure 2: Posttreatment Executive Function performance subtests adjusted for age, education, IMT, FSRP, visceral fat, and pretreatment performance. COWAT = controlled oral word association test. WL = weight loss and DASH group, DA = DASH-A group, CT = control group. * = significant at $p < .05$.

Examination of treatment effects on our Vigilance composite factor demonstrated

that both the combined DASH + WM ($F_{1,93} = 5.36, P = .023$) and DASH-A ($F_{1,93} = 4.51, P = .036$) groups exhibited improvement in Vigilance performance relative to controls, although this effect tended to be somewhat stronger among individuals in the DASH + WM group (Table 3) (Figure 3). The magnitude of effect was similar to that observed for our executive function composite, with both the DASH + WM (mean ES = 0.18, 95% CI = 0.02, 0.33) and DASH-A (mean ES = 0.15, 95% CI = 0.00, 0.30) groups improving in Vigilance relative to controls, who exhibited a small decrease in cognitive function (mean ES = -0.08, 95% CI = -0.23, 0.07). In addition to group assignment, greater baseline Vigilance performance, older age and higher FSRP levels were predictive of better posttreatment Vigilance (Table 5).

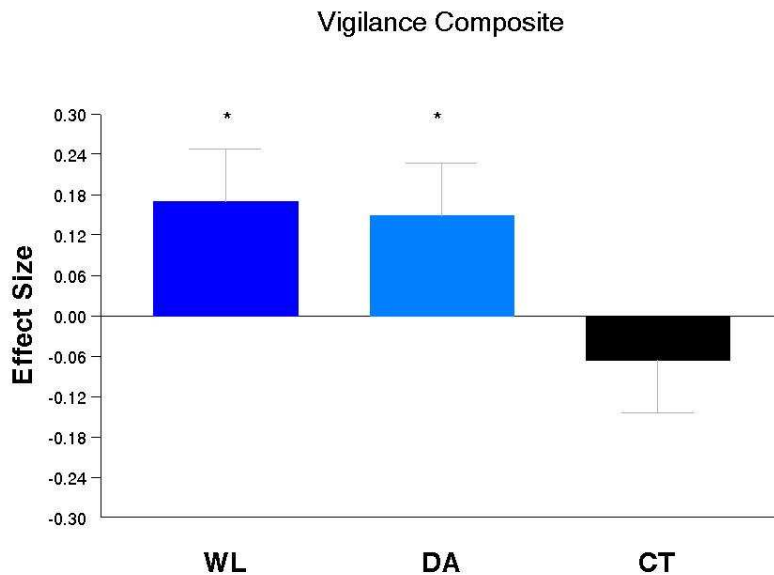


Figure 3: Posttreatment Vigilance performance adjusted for age, education, IMT, FSRP, visceral fat, and pretreatment performance. WL = DASH + WM

group, DA = DASH-A group, CT = control group. * = significant at $p < .05$.

Table 5: Effects of treatment and model covariates on vigilance. FSRP = Framingham Stroke Risk Profile; IMT = intima medial thickness. Regression coefficients are scaled by the interquartile range of the predictor variable. Regression coefficients can thus be interpreted as comparing a typical person in the middle of the upper half of the predictor distribution with a typical person in the middle of the lower half of the predictor distribution. † = $p \leq .10$; * = $p \leq .05$; ** = $p \leq .01$.

Predictor	Interquartile Range	Regression Coefficients
Baseline executive function	1.63	1.44**
Age, yrs	14.5	0.01
Education, yrs	4	0.06†
IMT, mm	0.16	-0.04
FSRP	2	0.10*
Visceral fat, %	10.1	0.07
DASH + WM vs. Control	1	0.26*
DASH-A vs. Control	1	0.23*

Examination of changes in individual neurocognitive measures (Figures 4)

demonstrated that both the DASH + WM ($F_{1,93} = 7.86, P = .006$) and DASH-A group ($F_{1,$

$93 = 5.51, P = .021$) group exhibited improvements in the Ruff 2 & 7 Test relative to

controls. In contrast, neither the DASH + WM ($F_{1,95} = 0.49, P = .486$) nor DASH-A groups ($F_{1,95} = 0.21, P = .651$) exhibited improvements on the digit symbol substitution test relative to controls.

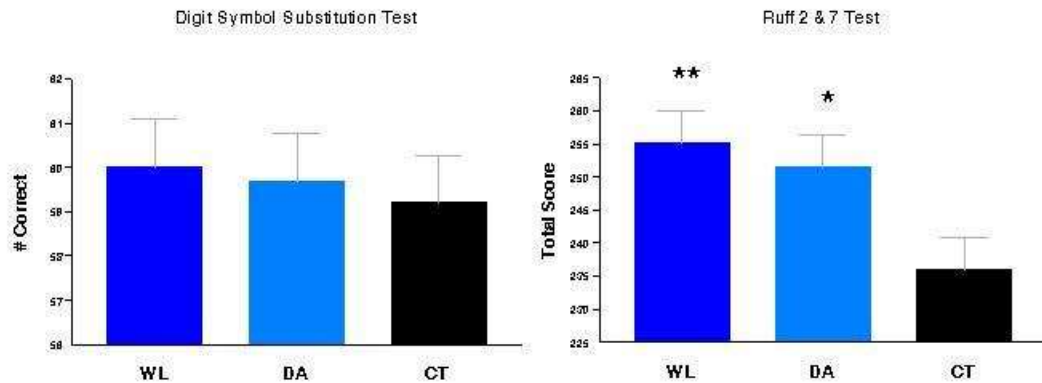


Figure 4: Posttreatment performance on Vigilance subtests adjusted for age, education, IMT, FSRP, visceral fat, and pretreatment performance. WL = DASH + WM group, DA = DASH-A group, CT = control group. * = significant at $p < .05$.

3.3.3 Moderators of Treatment Effects

Moderator analyses revealed a significant IMT by treatment group interaction for executive function ($F_{2,90} = 3.55, P = .033$). As shown in Figure 5, higher levels of IMT tended to be associated with reduced cognitive performance among participants in the control group ($r = -0.31, P = .077$), but were not associated with changes in cognitive performance among DASH-A participants ($r = -0.13, P = .460$). In contrast, higher IMT was associated with *greater* gains in executive function among participants in the DASH

+ WM group ($r = 0.38, P = .030$). Figure 5 shows that individuals with higher levels of IMT, a group at greater cardiovascular risk, improved to a greater extent in the DASH + WM group relative to either the DASH-A or control groups. Treatment effects on executive function were not moderated by baseline FSRP levels ($P = .782$), however. Similarly, neither IMT ($P = .354$) nor FSRP levels ($P = .862$) moderated the effects of treatment on our Vigilance factor.

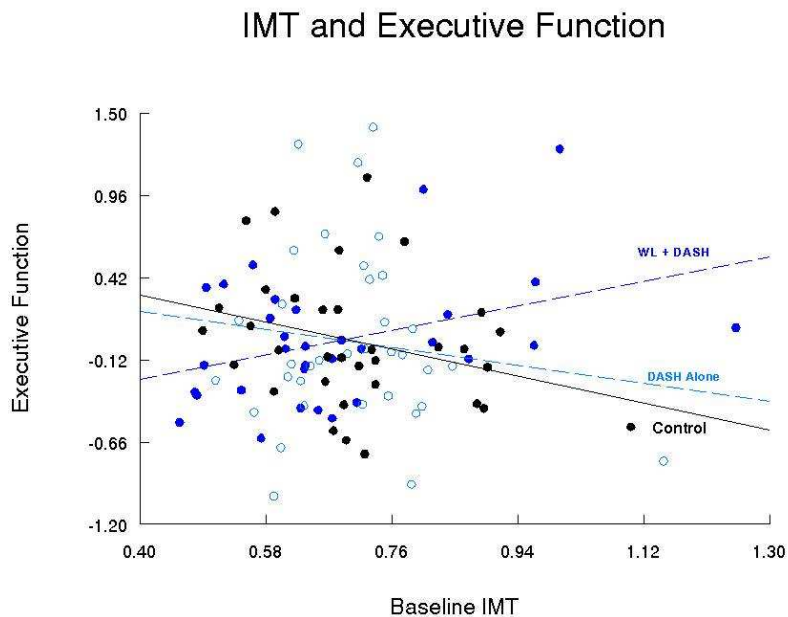


Figure 5: Baseline IMT by treatment group interaction. Participants with higher levels of IMT exhibited greater cognitive declines in the control group ($r = -0.31, P = .077$) and the DASH-A group ($r = -0.13, P = .460$), whereas participants with higher IMT exhibited cognitive gains in the DASH + WM group ($r = 0.38, P = .030$).

3.3.4 Mediators of Treatment Effects

Regression analyses demonstrated that the parameter estimates for the treatment group dummy variables associated with improvements in executive function were reduced once improved VO₂ was included in the model ($F_{1,88} = 4.96, P = .029$).

Specifically, the original parameter estimate for the Weight Loss + DASH group ($b = 0.35, P = .008$) was substantially reduced following the inclusion of changes in peak VO₂ were included in our model ($b = 0.10, P = .546$; Sobel $Z_{101} = 2.14, P = .032$). In contrast, neither reductions in weight (Sobel $Z_{101} = -0.62, P = .533$) nor reductions in SBP (Sobel $Z_{101} = 1.53, P = .126$) appeared to mediate the effects of treatment on executive function.

Examination of our vigilance variable demonstrated that weight reduction tended to attenuate the effects of treatment ($F_{1,92} = 3.69, P = .058$). Examination of dummy variables of treatment group variables showed that the parameter estimate for the DASH + WM group ($b = .26, P = .023$) was substantially reduced following inclusion of weight change ($b = -.09, P = .621$; Sobel $Z_{101} = 2.21, P = .027$) and tended to be attenuated after controlling for improvements in VO₂ ($b = 0.14, P = .344$; Sobel $Z_{101} = 1.72, P = .085$) in our model. In contrast, the parameter for the DASH + WM group was not significantly attenuated following inclusion of reductions in SBP ($b = .26, P = .032$; Sobel $Z_{101} = -0.13, P = .894$). When both VO₂ and weight loss were entered simultaneously into our regression model, weight loss emerged as the only significant mediator. Examination of the parameter estimate for treatment effects of the DASH-A group showed that this effect (b

= 0.23, $P = .036$) was not attenuated after controlling for weight reduction ($b = 0.20$, $P = .058$; Sobel $Z_{101} = 0.944$, $P = .345$), improvements in VO_2 ($b = .19$, $P = .061$; Sobel $Z_{101} = 0.72$, $P = .475$), or reductions in SBP ($b = .22$, $P = .038$; Sobel $Z_{101} = -0.13$, $P = .894$).

4. Discussion

Results from the present analysis indicate that a combined aerobic exercise and weight management intervention improves neurocognition among individuals with HBP. We found that a four month aerobic exercise and dietary modification program was associated with improved executive function and vigilance performance relative to controls. The effects of the combined intervention were particularly strong for individuals with higher levels of IMT at baseline, a group at increased risk of stroke and incident CHD. In addition, individuals assigned to receive dietary modification exhibited improved vigilance performance relative to controls, although executive function was not improved in this group. Mediator analyses demonstrated that improvements in executive function in the combined exercise and diet group were mediated by improved cardiorespiratory fitness, whereas improvements in vigilance performance were mediated by weight loss in this group. It is unclear what mediated the effects of the observed improvements in vigilance among the diet only group.

This is the first trial, to our knowledge, to examine the combined effects of aerobic exercise and dietary modification on cognitive function.

Although the combined effects of these interventions have not previously been investigated, multiple trials have examined the effects of aerobic exercise and diet separately as a means of improving cognitive function. The effects of aerobic exercise have been investigated extensively and are summarized in multiple meta-analytic reviews (van Uffelen, Chin, Hopman-Rock, & van, 2008a; Angevaren et al., 2008). The majority of extant reviews have found that aerobic exercise results in modest improvements in neurocognitive function (van Uffelen, Chin, Hopman-Rock, & van, 2008d), although many individual trials have reported small cognitive gains that did not achieve statistical significance (Etnier et al., 2006; Etnier J.L. et al., 1997), most likely as a result of inadequate statistical power. Colcombe and Kramer (Colcombe et al., 2003a) reported that RCTs of exercise are associated with clinically meaningful improvements in executive function, processing speed, memory, and motor function. Similarly, a recent Cochrane review (Angevaren et al., 2008) concluded that, although RCTs of aerobic exercise among individuals without cognitive impairment were associated with modest improvements in attentional processes, cognitive speed, and motor function. Most recently, van Uffelen and colleagues (van Uffelen, Chin, Hopman-Rock, & van, 2008c) reported that physical activity interventions among individuals without cognitive decline, on average, tended to report improved neurocognitive function. However, the authors noted that the majority of existing studies examining this question have failed to demonstrate a treatment benefit and that the extant literature is marked by a lack of

high-quality studies.

Interestingly, no studies, to our knowledge, have demonstrated that improvements in objective measures of fitness (i.e. peak VO₂) mediate improvements in cognitive function in the context of an RCT, although several trials have implicated improved aerobic fitness as a possible mediator of improvement (Kramer et al., 1999; Dustman et al., 1984). Etnier and colleagues (Etnier et al., 2006) have reviewed this association in two meta-analyses in which peak VO₂ was examined as a mediator of cognitive improvement. They found that, although higher levels of fitness were associated with better neurocognitive performance among cross-sectional study designs, studies examining pre-post comparisons found that larger gains in aerobic fitness were associated with *lesser* improvements in cognitive performance (Angevaren et al., 2008). Similarly, in Angevaren and colleagues' recent Cochrane review (Angevaren et al., 2008), the observed improvements in neurocognitive performance did not appear to be mediated by changes in cardiorespiratory fitness, as indexed by changes in peak VO₂. Thus, ours is the first study to demonstrate that hypothesized mediators of cognitive change are, in fact, associated with cognitive improvements in a randomized trial.

Our finding that peak VO₂ mediated the effects of treatment on cognitive function is consistent with previous cross-sectional (van Boxtel et al., 1997) and longitudinal studies (Etnier et al., 2001; Barnes et al., 2003), and has been implicated as a mediator in at least one RCT (Kramer et al., 1999). Improved peak VO₂ through exercise

training has been associated with better maintenance of white matter, as well as increasing gray matter brain volume in the anterior cingulate cortex, temporal gyrus, and areas of the frontal lobe in mechanistic trials (Colcombe et al., 2003b; Colcombe et al., 2006). Additionally, self-reported aerobic fitness has been associated with reduced functional anisotropy, an index of better white matter integrity (Marks et al., 2007). The efficiency of central oxygen consumption efficiency is an important determinant of cognitive performance (Eustache et al., 1995) and recent cross-sectional studies have demonstrated that peak VO_2 is associated with the efficiency of cerebral blood flow in older adults (Brown et al., 2008). Because cerebral white matter is particularly vulnerable to ischemia (Pantoni, Garcia, & Gutierrez, 1996; Murray et al., 2005), which has been associated with lower cardiorespiratory fitness (Ainslie et al., 2008), it is not surprising that improved fitness may reduce ischemic brain damage among patients with HBP (Dufouil et al., 2005).

Our finding that dietary modification using the DASH diet was associated with improved vigilance performance and that this improvement may have been mediated by reduced weight is novel and warrants further study. Although many previous trials have examined dietary changes to improve cognitive performance, the results have been considerably more varied, relative to the consistent, albeit weak, effects of aerobic exercise. Multiple trails have been conducted examining the effects of dietary supplementation with anti-oxidants (vitamins C and E) (Sano et al., 1997; Petersen et al.,

2005), vitamins B6 and B12, folate (Durga et al., 2007b; Martin et al., 2007; Kang et al., 2008), and fatty acids (Freund-Levi et al., 2006b) (Balk et al., 2007). Several recent trials have also examined the effects of reducing caloric intake as a means of enhancing neurocognitive performance (Witte et al., 2009; Martin et al., 2007). Trials of dietary supplementation have been equivocal, with notable exceptions (Durga et al., 2007a), and have been largely conducted among older adults at risk of cognitive decline. The existing literature on caloric restriction is more relevant to the present study, as these trials utilized changes in dietary *patterns*, as opposed to intake of specific nutrients, and were conducted among somewhat younger, often overweight, samples (Witte et al., 2009; Martin et al., 2007). In an RCT of 50 older adults at normal or overweight, Witte and colleagues (Witte et al., 2009) found that three months of caloric restriction resulted in improvements in memory performance and these changes were associated with decreased levels of fasting insulin and C-reactive protein. Notably, these results were strongest among subjects with the best adherence. Martin and colleagues (Spren & Strauss, 1991) conducted a similar study among 48 overweight adults, aged 25 to 50 years, in which participants were randomly assigned to either caloric restriction, caloric restriction and exercise, a low-calorie diet, or to a weight maintenance control group. Cognitive performance changed very little across any group and did not appear to be associated with changes in caloric intake or weight loss. The improvements observed with dietary modification in the current study may be best explained by differences in

sample characteristics, particularly with regards to BP status.

The finding that individuals with higher levels of IMT at baseline benefited to a greater extent in the combined aerobic exercise and diet group is consistent with a previous meta-analysis conducted by our research group, which indicated that compromised patient samples may exhibit greater cognitive benefits with aerobic exercise relative to samples among healthy, older adults (Smith et al., 2009). Specifically, we (Smith et al., 2009) found that exercise trials among individuals with MCI, a group at elevated risk for dementia and AD, were associated with greater improvements in memory relative other RCTs. It is also possible that individuals with more compromised cardiovascular functioning at baseline exhibited greater improvements in cardiovascular functioning since this group was lower at baseline relative to their healthier counterparts. The finding that FSRP levels did not moderate the effects of treatment in this study may be explained by the restricted range of stroke risk resulting from study inclusion criteria. Specifically, only one patient was diabetic, few patients reported tobacco use or heart disease, and the range of blood pressure values was limited to individuals with high normal blood pressure.

The present findings must be viewed with the following limitations in mind. First, our inclusion criteria limited our sample to individuals with mildly elevated SBP and who were able to actively engage in the aerobic exercise portion of the study protocol. It is therefore unclear how the present findings would have been affected by

the inclusion of individuals with greater cardiovascular comorbidities, including diabetes, or with limited mobility. Second, the use of general linear models to examine cognitive changes resulting from the intervention do not allow us to control for changes in cognitive performance due to autocorrelation between cognitive measures at baseline and posttreatment. It is therefore possible that the observed pattern of improvements were due to more rapid 'practice effects' of repeated administration of the measures, rather than improvement in neurocognition, per se. Third, it is possible that the observed improvements in cognitive function were also mediated by changes in inflammatory markers or growth factors not measured in the present study.

In conclusion, a combined dietary and aerobic exercise intervention improves neurocognitive performance among individuals with HTN and these effects may be pronounced among individuals with poorer vascular health. Dietary modification according to the DASH diet also appeared to improve certain neurocognitive functions. These treatment effects appear to be mediated by improved cardiorespiratory fitness and reduced weight. Future studies should examine the combined effects of dietary modification and aerobic exercise as a prophylactic treatment among older adults with HTN, a group at elevated risk for VaD. In addition, future studies would benefit from the collection of brain imaging data sensitive to changes in cerebral ischemia and white matter integrity in order to examine the effects of treatment on cerebral health.

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Biography

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