Effects of hypertension and diabetes mellitus on cognitive functioning: A profile analytic approach

by

Joy D. Humphreys Clark, M.A.

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Approved

Stephanie Harter

Sid E. O'Bryant

Joaquin Borrego, Jr.

Lee M. Cohen

John Lucas

Fred Hartmeister
Dean of Graduate School

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ABSTRACT

Research studies have demonstrated a relationship between several cardiovascular risk factors and decreased performance on cognitive tasks. In particular, recent research has suggested a strong effect of hypertension and diabetes mellitus on neuropsychological performance, particularly in certain cognitive domains, in both cognitively normal and demented individuals. Findings have been mixed, however, with some studies showing significant effects and others demonstrating none. Despite widely differing methodologies, all previous studies have had one thing in common: the examination of mean-group differences in performance on individual cognitive tests. The current study, conversely, investigated possible differences in neuropsychological profiles across several cognitive measures between cognitively normal individuals with and without hypertension and/or diabetes, as well as between individuals diagnosed with Alzheimer's disease with or without either condition. While effects of hypertension and diabetes on cognitive functioning were found in specific cognitive domains, current analyses did not find overall profile differences.

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CHAPTER I

INTRODUCTION

Studies have revealed a link between several medical conditions and decreased cognitive functioning. In particular, researchers have proposed links between cognitive impairment and conditions traditionally considered to be risk factors for cardiovascular disease, such as hyperlipidemia, atherosclerosis, and obesity (for reviews, see Launer, 2002; Messier, Awad, & Gagnon, 2004; Waldstein, Snow, Muldoon, & Katzel, 2001). These conditions are both treatable and preventable, and further exploration of their contributions to cognitive impairment may provide opportunities for prevention of cognitive decline and even the development of dementia. Furthermore, this line of research will provide practitioners with knowledge regarding what cognitive difficulties to expect among individuals with these particular conditions.

Hypertension and diabetes mellitus are two highly comorbid and prevalent vascular risk factors. Comorbodity rates of hypertension in individuals with diabetes range from 20% to 60%, and these conditions often co-occur as components of insulin resistance syndrome, also known as metabolic syndrome (American Diabetes Association, 2003). Particular attention in the literature has been paid to the risk of cognitive impairment among individuals with hypertension and/or diabetes mellitus, with studies revealing mixed results. While some studies have suggested that both hypertension and diabetes are related to decreased performance on cognitive tests, others have found no significant correlation between these conditions and cognitive impairment.

Hypertension and cognitive functioning

Hypertension is defined as systolic blood pressure (SBP) of 140 mmHg or greater and/or diastolic blood pressure (DBP) of 90 mmHg or greater as measured on two separate occasions (American Heart Association, 2007; Chobanian et al., 2003). This condition is a significant problem among adults in the United States. Prevalence of hypertension in the National Health and Nutrition Examination Survey conducted from 1999 to 2004 revealed a 67% prevalence rate among U.S. citizens aged 60 or older (Ostchega, Dillon, Hughes, Carroll, & Yoon, 2007). This study further revealed a significant increase in hypertension prevalence from 1988 to 2004.

Given the significant prevalence of hypertension, it is vital that its consequences, including effects on cognition, be understood. Along these lines, several studies have examined the relationship between hypertension and cognition. This condition does not appear to be associated with global impairments in cognition (Nilsson, Gullberg, Ekesbo, Von Schenck, & Gustafson, 1998); in fact, one study showed that higher scores on the Mini-Mental Status Examination (MMSE), a measure of global cognitive function, were correlated with higher SBP and DBP (Guo, Fratiglioni, Winblad, & Viitanen, 1997), although other factors, such as education or other sample characteristics, may have contributed to this finding. In addition, while the MMSE provides a basis for cognitive impairment screening, it is insensitive to mild or even moderate deficits in many cognitive domains. Thus, findings that hypertension in cognitively normal adults is not related to MMSE performance are not surprising given the measure's limitations.

Conversely, impairment in several individual cognitive domains has been associated with hypertension. In cross-sectional studies, the presence of hypertension has

been associated with lower scores on measures of executive functioning (Blumenthal, Madden, Pierce, Siegel, & Appelbaum, 1993; Kuo et al., 2005; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003), verbal memory (Elias et al., 1997; Elias, Elias, Wolf, & D'Agostino, 2003; Saxby et al., 2003), and visual memory (Andre-Petersson, Hagberg, Janzon, & Steen, 2001; Elias et al., 2003). One study showed that high DBP was associated with performance below the 50th percentile on tests of verbal memory, visual memory, and working memory, while increased levels of SBP were associated with performance below the 25th percentile on a test of verbal memory (Elias, D'Agostino, Elias, & Wolf, 1995). Hypertension appears to correlate with poorer cognitive performance even among individuals with dementia. Davis, Massman, and Doody (2003) found that among individuals with mild to moderate dementia, high DBP was associated with poorer performance on measures of verbal memory. Participants with AD and hypertension in a study by Reitz et al. (2007) performed more poorly on verbal fluency than those with AD only.

Longitudinal studies have suggested that higher blood pressure and hypertension are associated with increased risk for future cognitive impairment (Andre-Petersson et al., 2003; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Tzourio, Dufouil, Ducimetiere, & Alperovitch, 1999). According to Meyer, Rauch, Rauch, and Haque (2000), the odds ratio of cognitive decline associated with hypertension was 2.9 over an approximately six-year period. Other studies have found no association between high blood pressure at baseline and risk of cognitive decline at follow-up (Hebert et al., 2004; Insel, Palmer, Stroup-Benham, Markides, & Espino, 2005; Posner et al., 2002). Interestingly, Hebert et al. (2004) found a significant U-shaped relationship between DBP

and cognitive decline, whereby both highest and lowest levels of DBP at baseline were associated with increased risk of decline.

In addition to increased risk of cognitive decline, individuals with hypertension and elevated blood pressure may be at increased risk of the development of AD and other dementias. Li et al. (2007) demonstrated increased risk of dementia among younger individuals with high SBP; this association was not significant among older age groups. After controlling for relevant demographic and cardiovascular factors, Kivipelto et al. (2005) found a significantly increased risk for future development of AD among individuals with high blood pressure at midlife. In other studies, the effect of hypertension on risk for dementia was decreased after controlling for other cardiovascular risk factors, such as diabetes mellitus (Launer et al., 2000; Luchsinger et al., 2005).

Diabetes mellitus and cognitive functioning

According to the National Institute of Health (NIH, 2008), 10.7% of adults age 20 and older in the United States had diagnosed or undiagnosed diabetes in the year 2007; the prevalence rate rose to 23.1% among adults age 60 and older. This significant public health crisis led to a total of $174 billion in direct and indirect health costs in the last year. Diabetes mellitus is defined by the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (2002) as "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both" (p. S5). Diabetes has been divided into two types: individuals with Type 1 diabetes have a complete deficiency of insulin and are dependent upon insulin injections,

whereas Type 2 diabetes is the result of insulin resistance and inadequate compensation by the insulin secretory response and is normally associated with onset in adults. The majority of studies regarding the effects of diabetes on cognitive functioning have focused on type 2 diabetes mellitus. The diagnosis of Type 2 diabetes is made in the presence of the symptoms of diabetes (e.g., increasing thirst, lack of energy) in addition to a casual blood glucose concentration of greater than or equal to 200 mg/dl, fasting plasma glucose (defined as no caloric intake for eight hours) concentration of greater than or equal to 126 mg/dl, or plasma glucose of 200 mg/dl or greater two hours after glucose infusion.

Diabetes has been associated with impaired global cognitive functioning in cross-sectional studies (Debling, Amelang, Hasselbach, & Sturmer, 2006; Kuo et al., 2005; Wu et al., 2003). Deficits associated with diabetes appear to be most pronounced on measures of perceptual or processing speed (Arvanitakis et al., 2006; Kuo et al., 2005; Ryan & Geckle, 2000; U'Ren, Riddle, Lezak, & Bennington-Davis, 1990), verbal memory (Debling et al., 2006; Elias et al., 1997; Kuo et al., 2005; Van Harten et al., 2007), and motor speed (Van Harten et al., 2007). In the Religious Orders Study, an ongoing study involving longitudinal measures of cognitive function among a sample of nuns and priests, diabetes was associated with baseline impairment in episodic memory, semantic memory, working memory, and visuospatial ability (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004). Debling et al. (2006) found that individuals with diabetes were more likely to perform below the 25th percentile on measures of global cognition and verbal memory. Longitudinal studies suggest that baseline presence of diabetes is associated with increased risk of future cognitive decline in several cognitive

domains, including verbal fluency (Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004; Knopman et al., 2001) and complex attention (Kuo et al., 2005).

The presence of diabetes appears to constitute an even higher risk for AD and dementia than that associated with hypertension. Incidence of AD and dementia among individuals with diabetes at baseline is higher than that among individuals without diabetes at baseline (Arvanitakis et al., 2004; Leibson et al., 1997; Luchsinger et al., 2005; Xu, Qiu, Winblad, & Fratiglioni, 2007). The association between diabetes and increased risk for dementia appears to be greater among individuals without an apolipoprotein (ApoE) e4 allele (Akomolafe et al., 2006; Borenstein et al., 2005; Xu et al., 2007) as well as among those with hypertension (Xu, Qiu, Wahlin, Winblad, & Fratiglioni, 2004; Xu et al., 2007). Other studies have found associations between diabetes and increased risk for vascular dementia but not between diabetes and pure AD (MacKnight, Rockwood, Awalt, & McDowell, 2002; Peila, Rodriguez, & Launer, 2002). A recent study found a significantly increased risk of all-cause mild cognitive impairment (MCI) and amnestic MCI among individuals with baseline diabetes (Luchsinger et al., 2007). MCI is often considered a "pre-dementia" syndrome with a high conversion rate to both AD and vascular dementia.

Higher glucose levels and hyperinsulinemia in the absence of diabetes has also been associated with decreased cognitive functioning and increased risk for dementia. Kalmijn, Feskens, Launer, Stijnen, and Kromhout (1995) found that individuals with impaired glucose tolerance were more likely to have impaired cognitive function (as evidenced by MMSE scores below or equal to 23) than those with normal glucose tolerance. Sommerfield, Deary, and Frier (2004) raised the blood glucose levels of

individuals to 16.5 mmol/L ("hyperglycemic" condition) and compared their cognitive performance to that of individuals with blood glucose levels maintained at 4.5 mmol/L ("euglycemic" condition). The authors found that individuals in the hyperglycemic group performed more poorly on tests of processing speed and working memory than those in the euglycemic group. Hyperinsulinemia at baseline has also been associated with greater decline in performance on measures of delayed verbal recall and word fluency (Young, Mainous, & Carnemolla, 2006).

Differential impact of cardiovascular risk factors based on ethnicity

Research has consistently suggested that African Americans, both demented individuals and controls, suffer increased cognitive decline compared to Caucasians (Moody-Ayers, Mehta, Lindquist, Sands, & Covinsky, 2005). Reasons for ethnic differences may include differential rates of cardiovascular risk factors. African Americans have been found to have higher rates of many risk factors for dementia, including hypertension and diabetes (Moody-Ayers et al., 2005). Kramer et al. (2004) reported a 60% prevalence rate of hypertension in African Americans, a significantly higher rate than that of non-Hispanic whites (38%). Furthermore, rates of uncontrolled hypertension were higher in African Americans. Diabetes rates are also higher among African Americans. From 2004 to 2006, the prevalence rate of diagnosed diabetes was 11.8% among African Americans as compared to 6.6% of non-Hispanic whites (NIH, 2008). African Americans diagnosed with diabetes are furthermore less likely to exhibit good glycemic control (Saydah, Cowie, Eberhardt, De Rekeneire, & Narayan, 2007).

The impact of hypertension on cognitive performance appears to differ between ethnic groups. Hypertension has been found to affect cognitive functioning in African Americans with AD (Goldstein et al., 2005). Hebert et al. (2004) found that the influence of DBP on cognitive decline was stronger among Caucasians than African-Americans. Furthermore, Bohannon, Fillenbaum, Pieper, Hanlon, and Blazer (2002) showed that SBP had a significant U-shaped relationship with cognitive decline among Caucasian individuals; however, SBP was not significantly associated with cognitive decline among African-Americans. Another study found a stronger relationship between blood pressure and cognitive performance among African-Americans than Caucasians (Robbins, Elias, Elias, & Budge, 2005). Birns, Morris, Jarosz, Hugh, and Kalra (2008) found increased white matter damage resulting from hypertension in addition to poor performance on measures of executive function and verbal fluency among individuals of African-Caribbean descent compared to hypertensive Caucasians. The impact of diabetes on cognitive performance in African-Americans versus Caucasians has not been extensively studied in the literature, and, therefore, the differential impact of cardiovascular risk factors on cognitive performance between ethnic groups remains largely unclear.

Purpose

Overall, a review of the literature shows an association between the presence of hypertension and/or diabetes mellitus and cognitive impairment in specific cognitive domains. The majority of these studies, however, examined these associations through correlations with test scores and differences in group means. The practice of neuropsychology, on the other hand, involves the examination of profiles of cognitive

scores rather than scores on individual tests. For example, an individual who presents with memory impairments - a manifestation of a number of different disorders or diseases (e.g., Alzheimer's disease, vascular dementia, amnesia following traumatic brain injury) - is given a battery of tests to assess several aspects of cognition, including executive functioning, language, motor abilities, etc. The neuropsychologist then looks at the pattern of results to make conclusions regarding the patient's mental status, possible differential diagnoses, and treatment recommendations. Despite this standard practice, only a handful of known research studies have examined the neuropsychological profiles of scores on cognitive tests among different diagnostic groups. In particular, no studies have examined differences in neuropsychological profiles among individuals with hypertension and/or diabetes mellitus.

Profile analysis, a special case of multivariate analysis of variance (MANOVA) that allows for repeated measures, provides the opportunity to examine overall differences on neuropsychological profiles between groups; profile analysis further allows for comparison of scores on specific measures via post-hoc contrasts (Tabachnick & Fidell, 2000). Clinically-relevant information can thus be obtained from the profile analytic approach. Once clinicians are aware of the general pattern of cognitive performance underlying a particular medical condition, they will be more knowledgeable regarding what to expect cognitively from a patient that presents with that condition. Furthermore, an examination of patterns of cognitive performance may provide a basis for hypotheses regarding the biological mechanisms underlying these conditions as well as effected brain areas.

The purpose of the current study, therefore, is to examine neuropsychological profiles among individuals with hypertension and/or diabetes and determine whether these profiles differ according to hypertension and diabetes status. In order to examine whether the impact of hypertension or diabetes status differs according to dementia status, this study will examine cognitive profiles associated with the presence of hypertension or diabetes in nondemented controls, individuals with diagnosed AD, and individuals with diagnosed vascular dementia. In addition, given the literature suggesting differential impact of cardiovascular risk factors on cognitive functioning in different ethnic or racial groups, this study will examine potential differences in cognitive profile based on the presence of hypertension and diabetes in African-Americans versus Caucasians.

Primary aims and hypotheses

Primary Aim #1: To determine if neuropsychological profiles differ significantly between individuals with and without hypertension.

Hypothesis 1. After controlling for age and education, the cognitive profile of nondemented individuals with hypertension will differ significantly from the cognitive profile of nondemented individuals without hypertension. In addition, the cognitive profile of individuals diagnosed with AD or vascular dementia and hypertension will differ significantly from the cognitive profile of individuals diagnosed with AD or vascular dementia without hypertension. In particular, individuals with hypertension, regardless of dementia status, will perform more

poorly than individuals without hypertension in the domains of executive functioning, verbal memory, and visual memory.

Primary Aim #2: To determine if neuropsychological profiles differ significantly between individuals with and without diabetes mellitus.

Hypothesis 2. After controlling for age and education, the cognitive profile of nondemented individuals with diabetes mellitus will differ significantly from the cognitive profile of nondemented individuals without diabetes mellitus. In addition, the cognitive profile of individuals diagnosed with AD or vascular dementia and diabetes mellitus will differ significantly from the cognitive profile of individuals diagnosed with AD or vascular dementia without diabetes mellitus. In particular, individuals with diabetes mellitus, regardless of dementia status, will perform more poorly than individuals without diabetes mellitus in the domains of verbal memory, processing speed, and visuospatial ability.

Primary Aim #3: To determine if neuropsychological profiles differ significantly between individuals with both hypertension and diabetes mellitus and individuals with only one of these conditions or those with neither condition.

Hypothesis 3. After controlling for age and education, the cognitive profile of nondemented individuals with hypertension and diabetes mellitus will differ significantly from the cognitive profile of nondemented individuals with only

hypertension or diabetes mellitus. In addition, the cognitive profile of individuals diagnosed with AD or vascular dementia and hypertension and diabetes mellitus will differ significantly from the cognitive profile of individuals diagnosed with AD or vascular dementia with only hypertension or diabetes mellitus. In particular, individuals with both hypertension and diabetes mellitus, regardless of dementia status, will perform more poorly than individuals with only hypertension in the domains of verbal memory, processing speed, and visuospatial ability. Furthermore, individuals with both hypertension and diabetes mellitus, regardless of dementia status, will perform more poorly than individuals with only diabetes mellitus in the domains of verbal memory, visual memory, and executive functioning.

Hypothesis 4. After controlling for age and education, the cognitive profile of nondemented individuals with hypertension and diabetes mellitus will differ significantly from the cognitive profile of nondemented individuals with neither condition. In addition, the cognitive profile of individuals diagnosed with AD or vascular dementia and hypertension and diabetes mellitus will differ significantly from the cognitive profile of individuals diagnosed with AD or vascular dementia without hypertension and diabetes mellitus. In particular, individuals with hypertension and diabetes mellitus, regardless of dementia status, will perform more poorly than individuals without either condition in the domains of executive functioning, verbal memory, visual memory, processing speed, and visuospatial ability.

Primary Aim #4. To determine the impact of hypertension and diabetes mellitus among African Americans and Caucasians and to determine whether the impact of hypertension and diabetes mellitus differs according to ethnic group.

Hypothesis 5. After controlling for age and education, the cognitive profile of nondemented African American individuals with hypertension will differ significantly from the cognitive profile of nondemented African Americans without hypertension. In addition, the cognitive profile of nondemented Caucasians with hypertension will differ significantly from the cognitive profile of nondemented Caucasians without hypertension. The cognitive profile of nondemented African American individuals with hypertension will, furthermore, differ significantly from the cognitive profile of nondemented Caucasians with hypertension.

Hypothesis 6. After controlling for age and education, the cognitive profile of nondemented African American individuals with diabetes mellitus will differ significantly from the cognitive profile of nondemented African Americans without diabetes mellitus. In addition, the cognitive profile of nondemented Caucasians with diabetes mellitus will differ significantly from the cognitive profile of nondemented Caucasians without diabetes mellitus. The cognitive profile of nondemented African American individuals with diabetes mellitus will,

furthermore, differ significantly from the cognitive profile of nondemented Caucasians with diabetes mellitus.

Hypothesis 7. After controlling for age and education, the cognitive profile of nondemented African American individuals with diabetes mellitus and hypertension will differ significantly from the cognitive profile of nondemented African Americans with only hypertension or diabetes mellitus and nondemented African Americans with neither condition. In addition, after controlling for age and education, the cognitive profile of nondemented Caucasian individuals with diabetes mellitus and hypertension will differ significantly from the cognitive profile of nondemented Caucasians with only hypertension or diabetes mellitus and nondemented Caucasians with neither condition. The cognitive profile of nondemented African American individuals with hypertension and diabetes mellitus will, furthermore, differ significantly from the cognitive profile of nondemented Caucasians with hypertension and diabetes mellitus.

CHAPTER II

METHODS

Participants

Archival data from 3248 individuals aged 47 or older from the Mayo Clinic Alzheimer's Disease Research Center (ADRC) or Alzheimer's Disease Patient Registry (ADPR) were examined. Data included 899 individuals examined in Rochester, Minnesota, and classified as "cognitively normal"; 884 (98.3%) of these individuals identified their ethnicity as Caucasian, 8 (0.9%) as African American, 2 (0.2%) as American Indian, and 5 (0.5%) individuals did not report ethnicity. Another subsample of 1183 individuals classified as "cognitively normal" were examined in Jacksonville, Florida; of these, 770 (65.1%) identified their ethnicity as Caucasian, 396 (33.5%) as African American, 1 (0.1%) as American Indian and 16 (1.4%) individuals did not report ethnicity. Individuals diagnosed with probable AD include 838 individuals (782 Caucasians, 5 African Americans, 1 Asian, 1 American Indian, 49 with no ethnicity reported) examined in Rochester and 252 individuals (25 Caucasians, 203 African Americans, 1 Asian, 23 with no ethnicity reported) examined in Jacksonville. A group of 108 individuals (78 Caucasians, 25 African Americans, 5 with no ethnicity reported) from both sites diagnosed with vascular dementia were also examined.

Data were screened for missing variables, normality, and univariate and multivariate outliers. For details of data screening and outliers, please see Appendix B. Upon deletion of cases with missing data in addition to multivariate outliers, the final sample consisted of 1026 subjects. Of the final sample, 683 were classified as

cognitively normal, 299 were given a diagnosis of AD, and 44 were given a diagnosis of VaD.

Diagnoses were based on consensus agreement between neurologists, neuropsychologists, and a geriatrician based on evaluation of data from neuroimaging, laboratory results, and medical examinations. Data from neuropsychological testing was only examined after dementia was suspected; it was not utilized when determining normalcy. Individuals were classified as "cognitively normal" if they met the following criteria: (1) Self-, informant-, and physician-reported normal cognition, (2) informant report of intact ability to perform independent activities of daily living (IADLs), (3) absence of active central nervous system or psychiatric condition that could adversely affect cognition, (4) no use of psychoactive medications in doses sufficient to affect cognition, (5) any prior cognition-affecting medical conditions are no longer active and no residual effects are evident, and (6) any present medical conditions are noted by the physician as having no adverse effects on cognition. The diagnosis of AD was based on criteria of the National Institute of Neurological and Communicable Disease and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984), and vascular dementia was diagnosed based on criteria of the National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) International Workshop (Roman et al., 1993). For more details on these samples, diagnoses, and participant recruitment, see Graff-Radford et al. (2002), Lucas et al. (2005), Ivnik et al. (1992), and Testa et al. (2004).

Individuals were considered to have hypertension based upon self-report of diagnosis of hypertension by a physician and/or the presence of hypertension diagnostic codes in medical records. Similarly, individuals were considered to have diabetes mellitus based upon self-reported of diagnosis of diabetes by a physician and/or the presence of diabetes diagnostic codes in medical records.

Materials

Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975). The MMSE is a widely-used screening measure of cognitive status with an administration time of approximately five to ten minutes. Items assess orientation to place and time, attention/concentration, language, construction, and verbal recall. A score of less than 24 out of 30 is usually considered evidence of significant cognitive impairment, and Schmand et al. (1995) suggest that a five-point drop in MMSE score suggests significant cognitive decline from previous assessment. Original data suggest high 24-hour and 4-week test-retest reliability (Folstein et al., 1975). Scores on the MMSE are highly influenced by age and education (Marcopolous, McLain, & Giuliano, 1997; Uhlmann & Larson, 1991), as well as ethnicity (Bohnstedt, Fox, & Kohatsu, 1994; Espino, Lichtenstein, Palmer, & Hazuda, 2001).

Rey Auditory-Verbal Learning Test (AVLT; Rey, 1964). The AVLT is a measure of verbal learning and memory. Examinees are read a list of 15 unrelated words and asked to recall as many words as possible. This process is repeated five times, followed by the administration of a second "interference" word list. Examinees are then asked to

recall as many words as possible from the original word list both immediately and after an approximate 30-minute delay. A delayed recognition trial is also included. AVLT scores have been shown to successfully distinguish between normal controls and individuals with cognitive impairment (Powell, Cripe, & Dodrill, 1991); newer research also suggests that AVLT scores can be used to assess for preclinical AD (Estevez-Gonzalez, Kulisevsky, Boltes, Otermin, & Garcia-Sanchez, 2003). In addition, scores on the AVLT have demonstrated high test-retest reliability and convergent validity with similar verbal memory tests (Lezak, Howieson, & Loring, 2004; Strauss, Sherman, & Spreen, 2006).

Weschler Adult Intelligence Scale-Revised (WAIS-R; Weschler, 1981). Several subtests from the WAIS-R battery will be utilized in the current study: Information, Vocabulary, Arithmetic, Comprehension, Similarities, Picture Completion, Picture Arrangement, Object Assembly, Block Design, and Digit-Symbol Coding. The Information subtest assesses crystallized knowledge; the Vocabulary subtest is an assessment of verbal knowledge. The Similarities and Comprehension subtests similarly assesses verbal abilities and abstract reasoning. Picture Completion, Block Design, Picture Arrangement, and Object Assembly assess visual and abstract reasoning as well constructional abilities. Arithmetic and Digit-Symbol Coding incorporate processing speed, mathematic skills, and working memory. Reliability of the WAIS-R has been demonstrated in a psychiatric and neurologic clinical sample (Ryan, Prifitera, & Larsen, 1982), in a normal standardization sample (Matarazzo & Herman, 1984), and among individuals 75 years or older (Ryan, Paolo, & Brungardt, 1992).

Weschler Memory Scales-Revised (WMS-R; Wechsler, 1987). Four subtests from the WMS-R will be utilized in the current study: Logical Memory I and II and Visual Reproductions I and II. In Logical Memory I, examinees are read two short stories and asked to recall as many details from those stories as possible. After 30-minute delay, examinees are again asked to recall details from the previously heard stories (Logical Memory II). In Visual Reproductions I, examinees are briefly exposed to increasingly difficult line drawings and subsequently asked to reproduce the drawings without stimuli. After a 30-minute delay, examinees are again asked to reproduce these line drawings from memory (Visual Reproductions II). Scores obtained by patients with AD on the WMS are significantly lower than those obtained by normal controls (Efklides et al., 2002). Furthermore, performance profiles on the WMS-R have been shown to distinguish between patient populations in clinical settings (Lezak et al., 2004).

Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983). The BNT is a 60-item test of confrontational naming. Examinees are presented with a series of line drawings of common objects (e.g., tree, noose) and asked to name the objects. BNT scores have been used to successfully distinguish between individuals with AD from nondemented controls (Williams, Mack, & Henderson, 1989). Furthermore, scores on the BNT are highly correlated with verbal ability (Lezak et al., 2004) and demonstrate adequate test-retest reliability in neurologically normal subjects (Flanagan & Jackson, 1997).

Semantic Fluency (Animal, Fruit, Vegetable naming; Spreen & Strauss, 1998). In the semantic fluency test, examinees are given a limited amount of time to name as many objects belonging to a particular category (e.g., "animals") as possible. Semantic fluency impairments have been implicated in a number of neurological and psychiatric disorders, including Parkinson's disease (Henry & Crawford, 2004a) and schizophrenia (Bowie et al., 2004). In addition, poor performance on tests of semantic fluency is often associated with frontal lobe lesions, while impairments in semantic fluency relative to phonemic fluency are associated with Alzheimer's disease (Lezak et al., 2004). According to Strauss et al. (2006), evidence suggests that scores on semantic fluency tasks predict communication skills. Test-retest reliability is high (Strauss et al., 2006).

Controlled Oral Word Association Test (COWAT; Benton, Hamsher, & Sivan, 1994). The COWAT is a test of phonemic fluency in which the examinee is asked to give as many words beginning with a particular letter (C, F, or L) as possible within a one-minute time period. Phonemic fluency is sensitive to left frontal and temporal lobe lesions and is impaired in early stages of several dementing disorders, such as Parkinson's disease (Lezak et al., 2004). Scores on the COWAT have demonstrated high test-retest reliability (Tombaugh, Kozak, & Rees, 1999) and are highly correlated with verbal intelligence (Henry & Crawford, 2004b).

Mattis Dementia Rating Scale (DRS; Mattis, 1988). The Mattis Dementia Rating Scale is composed of five subtests (Attention, Initiation-Perseveration, Construction, Conceptualization, Memory) and a composite score. Scores on the DRS are highly

sensitive and specific for identifying Alzheimer's disease (van Gorp et al., 1999), and composite scores have been shown to be predictive of future institutionalization and mortality (Smith et al., 1994). Test-retest reliability is excellent (Lezak et al., 2004), and DRS scores demonstrate high correlations with similar dementia screening measures (Strauss et al., 2006).

Judgment of Line Orientation (JLO; Benton, Hannay, & Varney, 1975). The JLO is a test of visuoperceptual skills in which pairs of lines are matched to a display of several numbered lines arranged in a semi-circular pattern. Impaired performance on the JLO has been associated with several dementing disorders, including AD and Parkinson's disease (Strauss et al., 2006). Scores on this test demonstrate high internal consistency and adequate test-retest reliability (Lezak et al., 2004) and are correlated with WAIS-R visual subtests (Trahan, 1998).

Stroop Color-Word Test (Stroop; Golden, 1978). The Stroop Color-Word Test is a test of executive functioning and inhibition of response. Performance on the Stroop Color-Word Test is sensitive to effects of aging and declines in processing speed (Van der Elst, Van Broxtel, Van Breukelen, & Jolles, 2006). In addition, impaired performance on Stroop tasks may be useful for detecting early-stage AD (Bondi et al., 2002; Strauss et al., 2006). Scores on this measure demonstrate adequate to high reliability (Strauss et al., 2006).

Trail Making Test A & B (TMT; Reitan & Wolfson, 1985). TMT part A is a test of attention, visual scanning, and information processing speed; part B assesses processing speed as well as set-shifting abilities. Performance on the TMT is highly sensitive to executive functioning abilities as well as motor speed and attention (Lezak et al., 2004); performance is inversely correlated with age and the presence of dementia (Strauss et al., 2006). Reports of reliability coefficients are adequate to high depending upon the population studied (Spreen & Strauss, 1998).

Wide Range Achievement Test – 3rd edition (WRAT-3; Wilkinson, 1993). The Reading subtest of the WRAT is a measure of reading level and academic achievement; it is often used as a marker of educational quality or premorbid intelligence in brain damaged populations. According to Manly and colleagues (Manly, Jacobs, Touradji, Small, & Stern, 2002; Manly, Byrd, Touradji, & Stern, 2004), reading level is a better marker of premorbid abilities than years of education; furthermore, scores on the WRAT-3 Reading test serve to attenuate differences in cognitive tests related to ethnicity (Manly et al., 2002). Scores on the Reading subtest demonstrate high internal consistency and test-retest reliability (Strauss et al., 2006).

Data analyses

Dependent variables. Given the number of potential outcome variables provided by the extensive assessment battery described above, specific variables were selected prior to analysis. These measures, selected based upon data availability (several test scores were available for only a small number of participants),tapped various cognitive

domains, including verbal memory, visual memory, language, attention/processing speed, executive functioning, and visuoconstruction. Measures of verbal memory include immediate recall, delayed recall, and recognition trials of the AVLT and immediate and delayed recall trials of the WMS-R Logical Memory subtests, visual memory was assessed through scores on the immediate and delayed recall trials of the WMS-R Visual Reproduction subtests, and general memory abilities will be examined with the DRS Memory subtest. Scores on the BNT and COWAT were used to assess language functioning, while scores on the DRS Construction subtest were used to assess abilities within the visuoconstruction domain. Finally, attention/processing speed was examined through scores on the DRS Attention subtest, while executive functioning was assessed with the Initiation-Perseveration and Conceptualization subtests of the DRS.

Profile analysis. Profile analysis is an application of multivariate analysis of variance (MANOVA) that can be used to compare patterns of a set of dependent variables, such as scores on several measurements, between two or more groups (Tabachnick & Fidell, 2000). Profile analysis essentially asks whether "the two groups have the same pattern of means" on the dependent variables or measures (Tabachnick & Fidell, 2000, p. 391).

Several sets of profile analyses were run using SPSS General Linear Model to test hypotheses one through six. Profile analysis requires that all dependent variables be measured on the same scale; therefore, subjects' scores on all chosen variables were computed using the means and standard deviations of the cognitive normal group. Subsequently, subjects' z-scores on each variable were entered into the profile analyses

as dependent variables. Specifically, with z-scores entered as dependent variables, the first profile analysis included four groups, comparing the performance profile of all nondemented controls with hypertension only, nondemented controls with diabetes only, nondemented controls with both conditions, and nondemented controls with neither condition. Similar separate analyses were planned for individuals diagnosed with AD and those diagnosed with vascular dementia and for African-American and Caucasian nondemented controls. For hypotheses predicting differences between groups based on race, subjects in the cognitively normal group were categorized into groups based on race and disease status. All analyses were run controlling for the effects of age and education. Outcome variables examined included level differences (e.g., differences between the combined means of the groups), parallelism (e.g., asks if the differences between scores on separate assessments is the same for both groups), and flatness (e.g., difference from zero). Post-hoc analyses were utilized to determine specific differences in test scores between groups. All analyses were performed using SPSS.

CHAPTER III

RESULTS

Sample characteristics

For details of data screening and outliers, please see Appendix B. The final sample consisted of 1026 subjects (350 males, 676 females) with complete data, with a mean age and education level of 78.32 (SD = 7.71) and 12.76 (SD = 3.00), respectively. The sample was divided into three groups based upon diagnosis: cognitively normal (CN), Alzheimer's Disease (AD), and vascular dementia (VaD).

Profile analyses

Cognitively normal. The CN sample consisted of 683 subjects (225 males, 458 females) with a mean age and education level of 77.70 (SD = 7.80) and 13.02 (SD = 2.95), respectively. Self-identified race was Caucasian for 582 (85.2%) subjects and African American for 100 (14.6%); this information was missing for one (0.1%) remaining subject. Based on self-report or the presence of relevant diagnostic codes within medical records, 174 (25.5%) individuals in the CN group had no diagnosis of either hypertension or diabetes, 374 (54.8%) had a diagnosis of hypertension only, 41 (6.0%) had a diagnosis of diabetes only, and 94 (13.8%) cognitively normal subjects had a history of both conditions.

A profile analysis was performed on the selected subtests, with cognitively normal subjects divided into four subgroups: 1) those with neither hypertension or diabetes (CN-neither), 2) those with hypertension only (CN-HTN), 3) those with diabetes only (CN-DM), and 4) those with both conditions (CN-both). Data was examined for

violation of assumptions of profile analysis. Skewness and kurtosis were not significant at the $p < .01$ level for any of the dependent variables and thus the assumption of normality was not violated. Box's M test was significant; therefore, the assumption of homogeneity of variance-covariance was not met. Normally profile analysis is robust to homogeneity of variance-covariance; however, the discrepant sample sizes in the current analysis was of concern. Using methods described in Tabachnik and Fidell (2000), the variances and covariances were examined for each cell and were found to be larger in the smaller cells. Thus, the sizes of the four groups were equalized (n = 41) through random deletion of cases in SPSS. The profile analysis was performed on this final sample of 164 (63 males, 101 females), with a mean age of 76.21 (SD = 8.15) and mean education of 12.64 (2.91). In the final analysis, Mauchly's test of sphericity was significant, $\chi^2 = 463.98$, $p < .01$; therefore, the Greenhouse-Geisser sphericity correction was used.

The profiles of the four groups, shown in Figure 1, did not diverge significantly from parallelism, $F(28, 1478) = 1.02$, $p > .05$, $\eta^2 = 0.02$ (observed power = 0.88). Profiles collapsed across groups deviated significantly from flatness, $F(9, 1478) = 3.13$, $p < .01$, $\eta^2 = 0.02$ (observed power = 0.98); however, scores collapsed across tests did not differ significantly between groups, $F(3, 158) = 0.34$, $\eta^2 = 0.01$ (observed power = 0.12). Thus, there was only a significant main effect of test on test scores as would be expected given the diversity of the tests used. However, low power likely limited the ability to detect a significant main effect of disease group.

AD group. The AD group was comprised of 299 subjects (109 males, 190 females) with a mean age and education level of 79.61 (SD = 7.46) and 12.27 (SD =

2.98), respectively. Independent sample t-tests revealed significant differences between the AD and CN groups in both age (t = -3.57, p < .01) and education (t = 3.65, p < .01). Subjects in the AD group were significantly older and had less education than those in the CN group. Among subjects in the AD group, self-identified race included white (n = 281, 94.0%) and African American (n = 5, 1.7%); this data was missing for 13 (4.3%) additional subjects. Forty-nine (16.4%) individuals in the AD group had no diagnosis of either hypertension or diabetes, 173 (57.9%) had a diagnosis of hypertension only, 38 (12.7%) had a diagnosis of diabetes only, and 39 (13.0%) had a diagnosis of both conditions.

Similarly to the analyses above, a profile analysis was performed on the selected subtests, with AD subjects divided into four subgroups: 1) those with neither hypertension or diabetes (AD-neither), 2) those with hypertension only (AD-HTN), 3) those with diabetes only (AD-DM), and 4) those with both conditions (AD-both). Data were again examined for violation of assumptions. Neither skewness nor kurtosis was significant at the p < .01 level for any of the dependent variables; therefore, normality was assumed. Box's M was again significant, and larger variances and covariances were found in the large sample cells. The sizes of the four groups were thus equalized (n = 38) through random deletion of cases in SPSS. Profile analysis was performed on the final sample of 152 (68 males, 84 females) with a mean age of 79.52 (SD = 7.35) and mean education of 12.22 (SD = 3.01). In the final analysis, Mauchley's test of sphericity was significant, χ^2 = 1382.85, p < .01; thus, a Greenhouse-Geisser sphericity correction was used.

Profiles for the four groups deviated significantly from parallelism, $F(18, 898) = 1.65$, $p < .05$, $\eta^2 = 0.03$ (observed power = 0.95) but not flatness, $F(6, 898) = 1.32$, $p > .05$, $\eta^2 = 0.01$ (observed power = 0.53). There was no significant effect of group when scores were collapsed across tests, $F(3, 146) = 1.16$, $p > .05$ (observed power = 0.31). Again, insufficient power likely limited the ability to detect a significant main effect of group. To further examine the interaction of test with disease status, a series of post-hoc one-way ANOVAs were performed with Scheffe's corrected critical F ($F_s = 8.01$). Using this criterion, there were no significant differences between groups on any of the dependent variables. These findings underlie the small effect size for the interaction between disease status and test (i.e., parallelism).

VaD group. The VaD group was comprised of 44 subjects (16 males, 28 females) with a mean age and education level of 79.18 (SD = 6.98) and 12.18 (SD = 3.30), respectively. Subjects in the VaD group were not significantly older ($t = -1.23$, $p > .05$) nor did they have fewer years of education ($t = 1.80$, $p > .05$) than subjects in the cognitively normal group; in addition, neither age ($t = 0.360$, $p > .05$) nor education level ($t = 0.176$, $p < .05$) differed significantly between the VaD and AD groups. Please note, however, that the large discrepancy in sample sizes may have decreased power to detect a significant difference. Self-identified race in the VaD group included white (n = 42, 95.5%) and African American (n = 2, 4.5%). According to self-report and/or the presence of relevant diagnostic codes in medical records, five (11.4%) individuals within the VaD group had neither hypertension nor diabetes, 28 (63.6%) had hypertension only, 4 (9.1%) had diabetes only, and 7 (15.9%) had a history of both hypertension and

diabetes. The small numbers of subjects with VaD with neither condition, those with only diabetes, and those with both conditions precluded further analyses. Profile analysis requires that the n of the smallest group equal one more than the number of dependent variables. In the present analyses, the number of dependent variables was 14; therefore, planned analyses within the VaD group could not be performed.

African Americans. Within the cognitively normal group, 100 (27 males, 73 females) subjects identified themselves as African American. This subgroup had a mean age of 68.80 (SD = 7.82) and a mean education of 12.32 (SD = 3.39). Within this subgroup, 48 (48.0 %) subjects had a history of neither hypertension nor diabetes, 30 (30.0%) had a history of hypertension only, 5 (5.0%) had a history of diabetes only, and 17 (17.0%) had a history of both conditions. The small sample size of cognitively normal African Americans with diabetes only precluded analyses with this group. Therefore, only the CN-neither, CN-HTN, and CN-both groups were utilized in this analysis.

Data was examined for violation of assumptions of profile analysis. Skewness and kurtosis were not significant at the $p < .01$ level for any of the dependent variables, and thus the assumption of normality was met, as well as the assumption of homogeneity of variance-covariance, according to Box's M test ($F = 1.05$, $p > .05$). Mauchly's test of sphericity was significant, $\chi^2 = 463.98$, $p < .01$, and, therefore, the Greenhouse-Geisser sphericity correction was utilized.

Profiles of performance did not deviate significantly from parallelism, $F(15, 660) = 0.92$, $p > .05$, $\eta^2 = 0.02$ (observed power = 0.61), or flatness, $F(7, 660) = 1.79$, $p > .05$, $\eta^2 = 0.02$ (observed power = 0.74). Furthermore, the groups did not differ when scores

were collapsed across tests, $F(2, 90) = 2.43$, $p > .05$, $\eta^2 = 0.05$ (observed power = 0.48). These results suggest that among cognitively normal African Americans, hypertension and diabetes together or hypertension alone do not significantly affect scores on these cognitive tests when accounting for age and education. However, observed power in these analyses was not optimal and thus may have led to erroneous maintenance of the null hypotheses.

Caucasians. Within the cognitively normal group, 582 (197 males, 385 females) subjects identified their race as Caucasian. This subgroup had a mean age of 79.23 (SD = 6.71) and a mean education of 13.14 (SD = 2.86). Compared to cognitively normal African American individuals, Caucasians were significantly older, $t = 13.99$, $p < .01$, and had significantly more years of education, $t = 2.57$, $p = .01$. Within the Caucasian subgroup, 126 (21.6 %) subjects had no history of either hypertension or diabetes, 343 (30.0%) had a history of hypertension only, 36 (6.2%) had a history of diabetes only, and 77 (13.2%) had a history of both conditions.

A profile analysis was performed on the selected subtests, with Caucasian cognitively normal subjects divided into four subgroups: CN-neither, CN-HTN, CN-DM, and CN-both. Data was examined for violation of assumptions of profile analysis. Skewness and kurtosis were not significant at the $p < .01$ level for any of the dependent variables, and thus the assumption of normality was not violated. Neither was the assumption of homogeneity of variance-covariance violated, according to Box's M test. Mauchly's test of sphericity was significant, $\chi^2 = 1501.44$, $p < .01$; therefore, the Greenhouse-Geisser sphericity correction was used.

Profiles of the four groups, as shown in Figure 4, did not differ significantly from parallelism, $F(29, 5617) = 1.19$, $p > .05$, $\eta^2 = 0.01$ (observed power = 0.95). However, when collapsed across disease groups, profiles deviated significantly from flatness, $F(10, 5617) = 6.81$, $p < .01$, $\eta^2 = 0.01$ (observed power = 1.00). When collapsed across tests, scores did not differ by disease group, $F(3, 576) = 0.87$, $p > .05$, $\eta^2 = 0.01$, however power was insufficient (0.24). Thus, among cognitively normal Caucasians, profiles across selected cognitive measures do not differ by disease status. There is a main effect of test on scores which is not unexpected given the different domains measured.

Racial group comparisons. To examine whether the impact of hypertension and diabetes differs between racial groups, a profile analysis was performed comparing neuropsychological profiles between Caucasians and African Americans in each of the disease groups (i.e., CN-neither, CN-HTN, CN-both). In this analysis, profiles were examined between six groups: Caucasians with neither disease (CA-neither, n = 126), African Americans with neither disease (AA-neither, n = 48), Caucasians with hypertension only (CA-HTN, n =343), African Americans with hypertension only (AA-HTN, n = 30), Caucasians with both hypertension and diabetes (CA-both, n = 77), and African Americans with both hypertension and diabetes (AA-both, n = 18). As in the previous analyses with only African Americans, the diabetes only group was dropped due to inadequate sample size.

Data were again examined for violation of assumptions. Neither skewness nor kurtosis was significant at the $p < .01$ level for any of the dependent variables; therefore, normality was assumed. Box's M was significant and larger variances and covariances

were found in the large sample cells. The sizes of the six groups were thus equalized (n = 18) through random deletion of cases in SPSS. Profile analysis was performed on the final sample of 108 (32 males, 76 females) with a mean age of 74.40 (SD = 9.19) and mean education of 12.94 (SD = 3.46). In the final analysis, Mauchley's test of sphericity was significant, $\chi^2 = 608.15$, $p < .01$; thus, a Greenhouse-Geisser sphericity correction was used.

Profiles of the six groups, as shown in Figure 5, differed significantly from parallelism, $F(32, 638) = 1.51$, $p < .05$, $\eta^2 = 0.07$ (observed power = 0.99), but not from flatness, $F(6, 638) = 1.08$, $p > .05$, $\eta^2 = 0.01$ (observed power = 0.45). However, it should be noted that observed power for the flatness test was less than 50%; thus, it is possible that a significant effect would exist with a larger sample size. When collapsed across tests, scores did not differ significantly between groups, $F(5, 100) = 0.81$, $p > .05$, $\eta^2 = 0.04$. Again, however, observed power was very low (0.28).

To further examine differences between groups on the various tests, a series of one-way ANOVAs with each test as the dependent variable were run. To limit Type I error, Scheffe's critical F was utilized ($F_s = 11.50$). Based on this criterion, scores on none of the individual tests differed by group. Thus, groups categorized by race and disease status showed no significant differences on a range of cognitive tests; however, overall profiles based on race and disease status did differ significantly from one another.

Follow-up regression analyses

While the above analyses found insignificant results when comparing cognitive profiles between individuals with or without hypertension and/or diabetes, previous

research has suggested that these conditions do affect scores on individual cognitive tests. The link between these diseases and cognitive functioning remains unclear. Therefore, a series of multiple regression analyses were included to determine whether there are any significant links between cognition and these cardiovascular risk factors regardless of overall profiles.

A series of hierarchical linear regression analyses were run among cognitively normal individuals with scores on each cognitive test as the dependent variable. Because regression is robust to differences in measurement scale, original cognitive scores rather than standardized z-scores were utilized. Age and education were entered at Step 1, followed by hypertension and diabetes status at Step 2. After controlling for age and education, the presence of diabetes, but not hypertension, was significantly predictive of lower scores on the AVLT Immediate Recall trial, accounting for 8.3% of the total variance. On WMS-R Logical Memory I, there was a trend toward significance for hypertension, but not for diabetes. Hypertension accounted for 7.4% of the total variance in predicting Logical Memory I scores. There was also a trend toward significance of hypertension status in predicting WMS-R Visual Reproduction I and II, with hypertension accounting for 7.3% and 7.2% of the total variance, respectively; diabetes was not a significant predictor. Interestingly, the presence of hypertension significantly predicted higher scores on the Boston Naming Test, accounting for 12.4% of the total variance in test scores; again, diabetes was not a significant predictor. When predicting scores on DRS Construction, diabetes, but not hypertension, was a significant predictor, accounting for 8.1% of the total variance. These findings, however, differed once a Bonferroni correction was used, in which the family-wise alpha rate was distributed

across all fourteen comparisons (significance was considered at $\alpha = 0.004$). Only the effect of hypertension on Boston Naming Test scores remained significant. Neither hypertension nor diabetes were significantly predictive of scores on other cognitive measures, including AVLT Delayed Recall and Recognition, WMS-R Logical Memory II, COWAT, DRS Attention, DRS Initiation-Perseveration, DRS Conceptualization, and DRS Memory among cognitively normal subjects. Overall, these findings suggest that the presence of diabetes among cognitively normal older adults is related to poorer scores on tests of visuoconstruction and immediate verbal memory when stimuli are presented in list-fashion. On the other hand, hypertension is only significantly related to higher scores on confrontational naming tasks; however, trends suggest that hypertension may be related to lower scores on immediate verbal memory for stories and visual memory, although neither is significant. These findings, however, do not hold under a more conservative alpha level. See Table 4 for more information on all regression analyses.

Similar analyses were run among individuals in the AD group. After controlling for age and education, hypertension, but not diabetes, was associated with lower scores on AVLT Immediate Recall, accounting for 14.5% of the total variance. On AVLT Delayed Recall, both diabetes and hypertension were significant individual predictors, accounting for 16.3% and 12.1% of the total variance, respectively. Interestingly, diabetes was associated with higher AVLT Delayed Recall scores, while hypertension was associated with lower scores. Both hypertension and diabetes were associated with higher scores on WMS-R Visual Reproduction II, accounting for 12.0% and 23.3% of the total variance, respectively. Hypertension, not diabetes, was also a significant individual predictor of lower scores on COWAT, accounting for 14.5% of the total variance.

Diabetes was significantly predictive of lower DRS Attention and higher DRS Memory scores, accounting for 12.2% and 14.4% of the total variance, respectively, while hypertension was significantly predictive of lower scores on DRS Initiation-Perseveration, accounting for 14.9% of the total variance. Once the Bonferroni correction was applied, however, only the effect of diabetes on WMS-R Visual Reproduction II remained, while the effect of diabetes on AVLT Delayed Recall was marginally significant. Neither diabetes nor hypertension was associated with scores on the remaining cognitive tests. Overall, these scores suggest that the presence of diabetes significantly predicts lower scores on tests of attention and higher scores on tests of verbal and visual memory among individuals with AD. Hypertension, conversely, is predictive of lower scores on tasks of verbal fluency and executive functioning and higher scores on delayed recall of visual information. Again, however, these findings do not hold under a more conservative alpha level. See Table 4 for more information on these analyses.

To further explore the effects of hypertension and diabetes based on ethnicity, these analyses were repeated with individuals in the CN group divided in Caucasian and African American. Among cognitively normal Caucasians, diabetes was a significant individual predictor for lower scores on AVLT Immediate Recall, accounting for 9.1% of the total variance; COWAT, 8.2%; and DRS Construction, 8.4%. Once the Bonferroni correction was applied, these effects were no longer significant. Hypertension was not a significant predictor of cognitive performance on any of the dependent measures among cognitively normal Caucasians. Among cognitively normal African Americans, there was a trend toward significance of hypertension on higher scores on WMS-R Visual

Reproduction II, accounting for 19.3% of the total variance and a trend toward significance of diabetes on lower scores on DRS Construction, accounting for 19.8% of the total variance. There were no significant effects of hypertension or diabetes on any of the remaining cognitive measures. These scores suggest that the effects of diabetes on measures of immediate verbal memory, verbal fluency, and visuoconstruction are restricted to Caucasians. However, it should be noted that power to detect a significant effect was much higher among Caucasians than among African Americans; furthermore, the effects of diabetes within the Caucasian sample did not hold up under a more conservative alpha level. See Table 5 for further information on these analyses.

Table 1. Regression equations predicting cognitive test scores for the cognitively normal group

Step 1

		Age		Education	
Test	R^2	β	Pr^2	β	Pr^2
AVLT IR	0.08**	-0.24**	0.24	0.15**	0.15
AVLT DR	0.09**	-0.25**	0.25	0.16**	0.17
AVLT Rec	0.03**	-0.17**	0.17	0.02	0.02
WMS LM I	0.13**	-0.24**	0.25	0.26**	0.27
WMS LM II	0.12**	-0.21**	0.22	0.28**	0.29
WMS VR I	0.13**	-0.30**	0.31	0.19**	0.20
WMS VR II	0.13**	-0.24**	0.25	0.27**	0.28
BNT	0.13**	-0.13**	0.14	0.33**	0.33
COWAT	0.10**	-0.01	0.01	0.32**	0.32
DRS Att	0.07**	-0.17**	0.17	0.19**	0.20
DRS I-P	0.05**	-0.14**	0.14	0.16**	0.16
DRS Cons	0.03**	0.11**	0.12	0.13**	0.13
DRS Conc	0.13**	-0.12**	0.13	0.33**	0.33
DRS Mem	0.07**	-0.24**	0.24	0.12**	0.12

Step 2

		Age		Education		DM status		HTN status	
Test	R^2†	β	Pr^2	β	Pr^2	β	Pr^2	β	Pr^2
AVLT IR	0.05*	-0.12*	0.12	0.06	0.06	-0.01	0.01	-0.15*	0.15
AVLT DR	0.07**	0.03	0.03	0.12*	0.12	0.17**	0.16	-0.12*	0.12
AVLT Rec	0.01	-0.01	0.01	0.08	0.08	0.05	0.04	-0.02	0.02
WMS LM I	0.12	-0.15**	0.15	0.29**	0.29	-0.01	0.01	-0.10	0.10
WMS LM II	0.11	-0.16**	0.17	0.26**	0.27	0.09	0.09	-0.05	0.05
WMS VR I	0.04	-0.12**	0.12	0.12*	0.12	0.02	0.02	-0.04	0.04
WMS VR II	0.10**	-0.10	0.11	0.21**	0.21	0.24**	0.23	0.12*	0.12
BNT	0.12	-0.26**	0.26	0.20**	0.21	0.09	0.09	-0.02	0.02
COWAT	0.11*	-0.04	0.04	0.29**	0.29	-0.10	0.10	-0.14*	0.15
DRS Att	0.06	-0.02	0.02	0.19**	0.19	-0.12*	0.12	-0.10	0.10
DRS I-P	0.06*	-0.10	0.10	0.15*	0.15	-0.06	0.06	-0.15*	0.15
DRS Cons	0.05	-0.04	0.04	0.18**	0.18	-0.08	0.08	-0.06	0.06
DRS Conc	0.16	-0.08	0.08	0.39**	0.39	-0.03	0.04	-0.02	0.02
DRS Mem	0.10*	-0.19**	0.19	0.21**	0.22	0.14*	0.14	0.06	0.06

Note: $*p < .05$, $**p < .01$, $***p < .004$, †change in R^2 from Step 1, pr^2 = partial correlation, AVLT = Auditory Verbal Learning Test, IR = Immediate Recall, DR = Delayed Recall, Rec = Recognition, WMS = Wechsler Memory Scale-Revised, LM = Logical Memory, VR = Visual Reproduction, BNT = Boston Naming Test, COWAT = Controlled Oral Word Association Test, DRS = Dementia Rating Scale, Att = Attention, I-P = Initiation-Perseveration, Cons = Construction, Conc = Conceptualization, Mem = Memory

Table 2. Regression equations predicting cognitive test scores for the Alzheimer's group

Step 1

		Age		Education	
Test	R^2	β	Pr^2	β	Pr^2
AVLT IR	0.02*	-0.14*	0.14	0.06	0.06
AVLT DR	0.01	0.02	0.02	0.11	0.11
AVLT Rec	0.01	-0.02	0.02	0.08	0.08
WMS LM I	0.11**	-0.16**	0.17	0.28**	0.29
WMS LM II	0.10**	-0.17**	0.17	0.26**	0.26
WMS VR I	0.03**	-0.13*	0.13	0.12*	0.12
WMS VR II	0.05**	-0.09	0.09	0.20**	0.20
BNT	0.11**	-0.26**	0.26	0.20**	0.20
COWAT	0.09**	-0.06	0.06	0.29**	0.29
DRS Att	0.04**	-0.03	0.03	0.19**	0.19
DRS I-P	0.03**	-0.12*	0.12	0.14*	0.15
DRS Cons	0.04**	-0.05	0.05	0.18**	0.18
DRS Conc	0.16**	-0.08	0.09	0.39**	0.39
DRS Mem	0.08**	-0.18**	0.18	0.21**	0.21

Step 2

		Age		Education		DM status		HTN status	
Test	R^2†	β	Pr^2	β	Pr^2	β	Pr^2	β	Pr^2
AVLT IR	0.05*	-0.12*	0.12	0.06	0.06	-0.01	0.01	-0.15*	0.15
AVLT DR	0.07**	0.03	0.03	0.12*	0.12	0.17**	0.16	-0.12*	0.12
AVLT Rec	0.01	-0.01	0.01	0.08	0.08	0.05	0.04	-0.02	0.02
WMS LM I	0.12	-0.15**	0.15	0.29**	0.29	-0.01	0.01	-0.10	0.10
WMS LM II	0.11	-0.16**	0.17	0.26**	0.27	0.09	0.09	-0.05	0.05
WMS VR I	0.04	-0.12*	0.12	0.12*	0.12	0.02	0.02	-0.04	0.04
WMS VR II	0.10**	-0.10	0.11	0.21**	0.21	0.24**	0.23	0.12*	0.12
BNT	0.12	-0.26**	0.26	0.20**	0.21	0.09	0.09	-0.02	0.02
COWAT	0.11*	-0.04	0.04	0.29**	0.29	-0.10	0.10	-0.14*	0.15
DRS Att	0.06	-0.02	0.02	0.19**	0.19	-0.12*	0.12	-0.10	0.10
DRS I-P	0.06*	-0.10	0.10	0.15*	0.15	-0.06	0.06	-0.15*	0.15
DRS Cons	0.05	-0.04	0.04	0.18**	0.18	-0.08	0.08	-0.06	0.06
DRS Conc	0.16	-0.08	0.08	0.39**	0.39	-0.03	0.04	-0.02	0.02
DRS Mem	0.10*	-0.19**	0.19	0.21**	0.22	0.14*	0.14	0.06	0.06

Note: $*p < .05$, $**p < .01$, $***p < .004$, †change in R^2 from Step 1, pr^2 = partial correlation, AVLT = Auditory Verbal Learning Test, IR = Immediate Recall, DR = Delayed Recall, Rec = Recognition, WMS = Wechsler Memory Scale-Revised, LM = Logical Memory, VR = Visual Reproduction, BNT = Boston Naming Test, COWAT = Controlled Oral Word Association Test, DRS = Dementia Rating Scale, Att = Attention, I-P = Initiation-Perseveration, Cons = Construction, Conc = Conceptualization, Mem = Memory

Table 3. Regression equations predicting cognitive test scores among Caucasians in the cognitively normal group

Step 1

		Age		Education	
Test	R^2	β	Pr^2	β	Pr^2
AVLT IR	0.08**	-0.25**	0.25	0.12**	0.12
AVLT DR	0.09**	-0.26**	0.27	0.13**	0.14
AVLT Rec	0.02**	-0.13**	0.13	0.02	0.02
WMS LM I	0.19**	-0.36**	0.37	0.23**	0.25
WMS LM II	0.14**	-0.27**	0.28	0.25**	0.26
WMS VR I	0.20**	-0.41**	0.42	0.16**	0.18
WMS VR II	0.15**	-0.28**	0.29	0.25**	0.26
BNT	0.19**	-0.35**	0.36	0.24**	0.25
COWAT	0.08**	-0.04	0.04	0.28**	0.28
DRS Att	0.08**	-0.19**	0.19	0.19**	0.19
DRS I-P	0.05**	-0.17**	0.17	0.14**	0.15
DRS Cons	0.02*	-0.09*	0.09	0.09*	0.09
DRS Conc	0.16**	-0.26**	0.27	0.30**	0.31
DRS Mem	0.08**	-0.25**	0.26	0.10*	0.10

Step 2

		Age		Education		DM status		HTN status	
Test	R^2†	β	Pr^2	β	Pr^2	β	Pr^2	β	Pr^2
AVLT IR	0.09	-0.26**	0.26	0.11**	0.11	-0.09*	0.09	0.00	0.00
AVLT DR	0.09	-0.27**	0.27	0.13**	0.13	-0.06	0.06	-0.02	0.02
AVLT Rec	0.02	-0.13**	0.13	0.02	0.02	-0.02	0.02	-0.01	0.01
WMS LM I	0.19	-0.36**	0.36	0.23**	0.25	0.01	0.01	0.02	0.03
WMS LM II	0.14	-0.26**	0.27	0.25**	0.26	0.03	0.04	0.01	0.01
WMS VR I	0.21	-0.42**	0.42	0.16**	0.17	-0.02	0.02	0.02	0.02
WMS VR II	0.15	-0.27**	0.28	0.25**	0.26	0.05	0.06	0.03	0.03
BNT	0.19	-0.34**	0.35	0.24**	0.25	0.02	0.02	0.06	0.07
COWAT	0.09*	-0.05	0.05	0.27**	0.28	-0.08*	0.08	0.06	0.06
DRS Att	0.08	-0.19**	0.19	0.19**	0.19	-0.01	0.01	-0.05	0.05
DRS I-P	0.06	-0.17**	0.17	0.14**	0.14	0.00	0.00	0.06	0.06
DRS Cons	0.02	-0.10*	0.10	0.08	0.08	-0.09*	0.08	0.01	0.01
DRS Conc	0.16	-0.26**	0.27	0.30**	0.31	-0.01	0.01	-0.01	0.01
DRS Mem	0.08	-0.25**	0.25	0.10*	0.11	0.02	0.03	-0.01	0.01

Note: *$p < .05$, **$p < .01$, †change in R^2 from Step 1, pr^2 = partial correlation, AVLT = Auditory Verbal Learning Test, IR = Immediate Recall, DR = Delayed Recall, Rec = Recognition, WMS = Wechsler Memory Scale-Revised, LM = Logical Memory, VR = Visual Reproduction, BNT = Boston Naming Test, COWAT = Controlled Oral Word Association Test, DRS = Dementia Rating Scale, Att = Attention, I-P = Initiation-Perseveration, Cons = Construction, Conc = Conceptualization, Mem = Memory

Table 4. Regression equations predicting cognitive test scores among African Americans in the cognitively normal group

Step 1

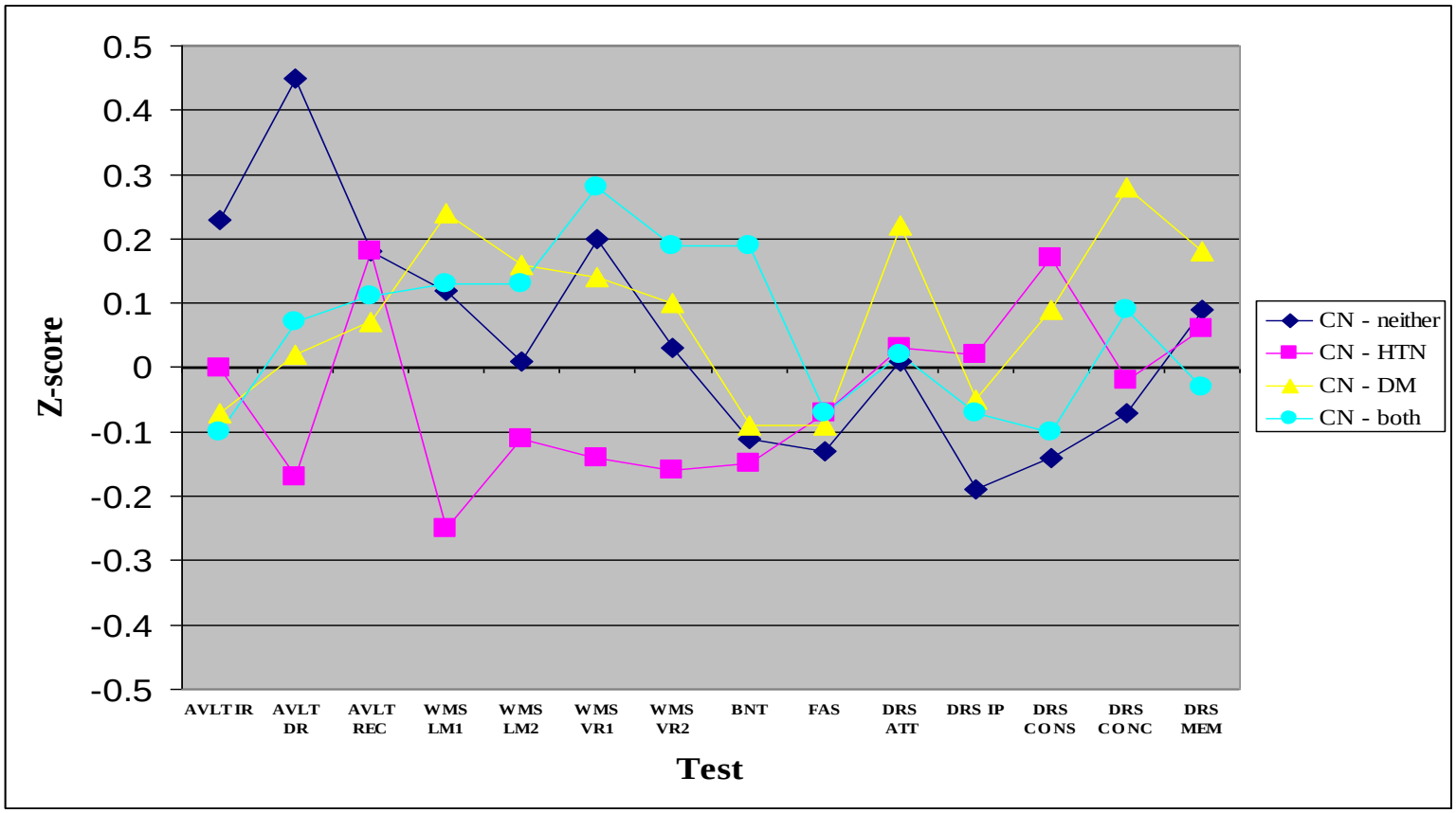
		Age		Education	
Test	R^2	β	Pr^2	β	Pr^2
AVLT IR	0.10**	-0.21*	0.22	0.23*	0.24
AVLT DR	0.13**	-0.29**	0.29	0.21*	0.22
AVLT Rec	0.05	-0.22*	0.22	0.03	0.03
WMS LM I	0.09**	-0.17	0.18	0.24*	0.25
WMS LM II	0.20**	-0.29**	0.30	0.32**	0.34
WMS VR I	0.06*	-0.18	0.18	0.17	0.17
WMS VR II	0.18**	-0.27**	0.29	0.32**	0.33
BNT	0.30**	-0.15	0.17	0.52**	0.53
COWAT	0.22**	-0.09	0.10	0.46**	0.46
DRS Att	0.08*	-0.23*	024	0.14	0.15
DRS I-P	0.05	0.01	0.01	0.23*	0.23
DRS Cons	0.02	0.03	0.03	0.14	0.14
DRS Conc	0.15**	-0.14	0.15	0.36**	0.36
DRS Mem	0.06*	-0.20*	0.20	0.13	0.13

Step 2

		Age		Education		DM status		HTN status	
Test	R^2†	β	Pr^2	β	Pr^2	β	Pr^2	β	Pr^2
AVLT IR	0.11	-0.23*	0.23	0.24*	0.24	-0.09	0.09	0.04	0.04
AVLT DR	0.15	-0.28**	0.29	0.21*	0.22	-0.09	0.09	-0.07	0.07
AVLT Rec	0.05	-0.21*	0.20	0.03	0.03	0.02	0.02	-0.06	0.06
WMS LM I	0.11	-0.19	0.20	0.25*	0.26	-0.09	0.09	0.12	0.12
WMS LM II	0.20	-0.29**	0.31	0.32**	0.34	0.03	0.03	0.07	0.08
WMS VR I	0.08	-0.20	0.20	0.17	0.18	-0.05	0.05	0.12	0.12
WMS VR II	0.21	-0.30**	0.32	0.33**	0.34	-0.07	0.07	0.19	0.19
BNT	0.32	-0.17*	0.20	0.53**	0.54	-0.10	0.12	0.12	0.14
COWAT	0.23	-0.10	0.10	0.46**	0.46	-0.03	0.03	0.06	0.07
DRS Att	0.10	-0.25*	0.25	0.15	0.15	0.00	0.00	0.15	0.14
DRS I-P	0.06	-0.01	0.01	0.24*	0.24	-0.06	0.06	0.09	0.08
DRS Cons	0.06	-0.01	0.01	0.15	0.15	-0.21	0.20	0.11	0.11
DRS Conc	0.17	-0.15	0.16	0.36**	0.37	0.01	0.01	0.12	0.12
DRS Mem	0.07	-0.22*	0.22	0.13	0.14	-0.12	0.12	0.06	0.06

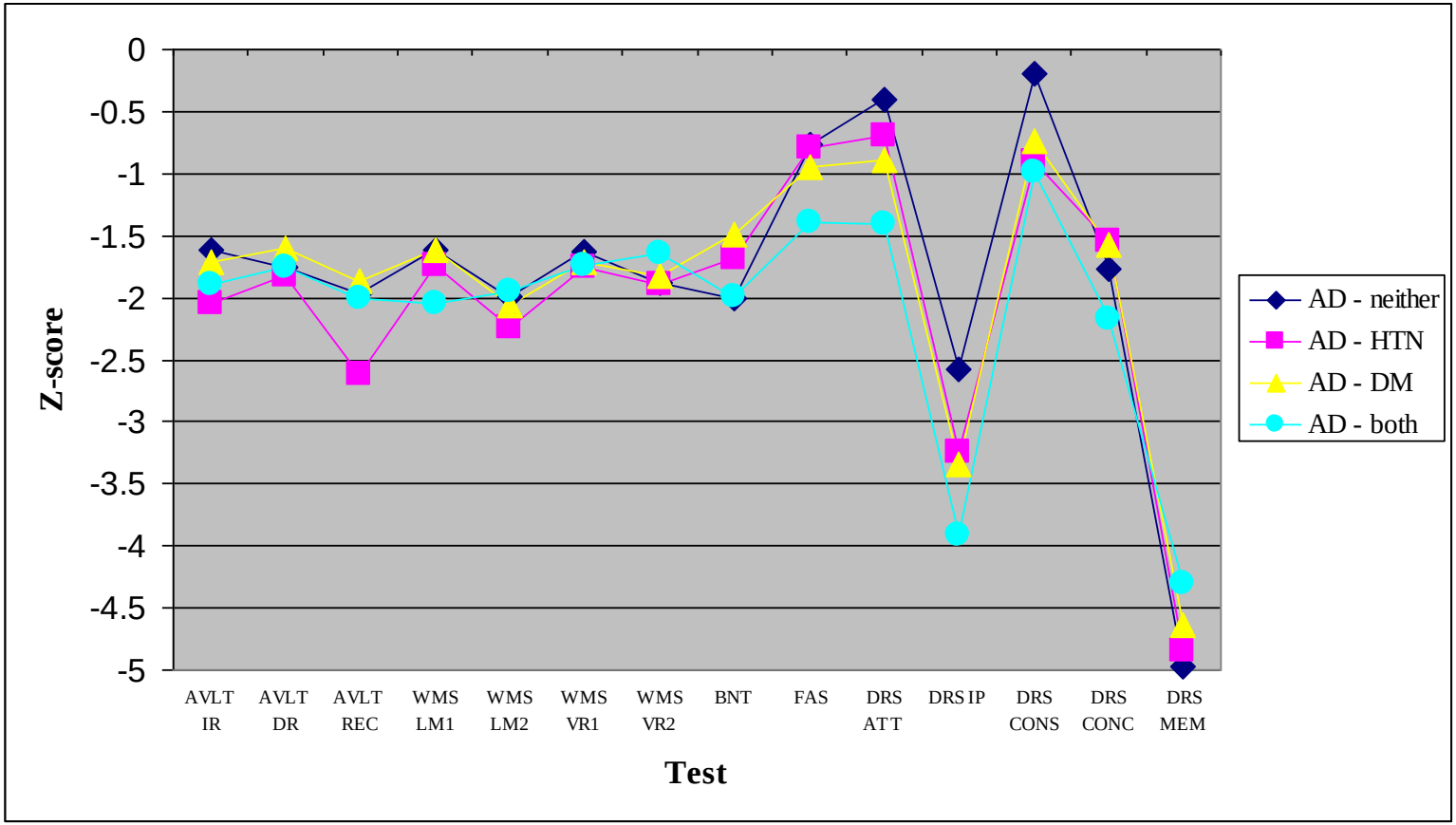
Note: $*p < .05$, $**p < .01$, †change in R^2 from Step 1, pr^2 = partial correlation, AVLT = Auditory Verbal Learning Test, IR = Immediate Recall, DR = Delayed Recall, Rec = Recognition, WMS = Wechsler Memory Scale-Revised, LM = Logical Memory, VR = Visual Reproduction, BNT = Boston Naming Test, COWAT = Controlled Oral Word Association Test, DRS = Dementia Rating Scale, Att = Attention, I-P = Initiation-Perseveration, Cons = Construction, Conc = Conceptualization, Mem = Memor

Figure 1. *Profile analysis – Cognitively normal sample*



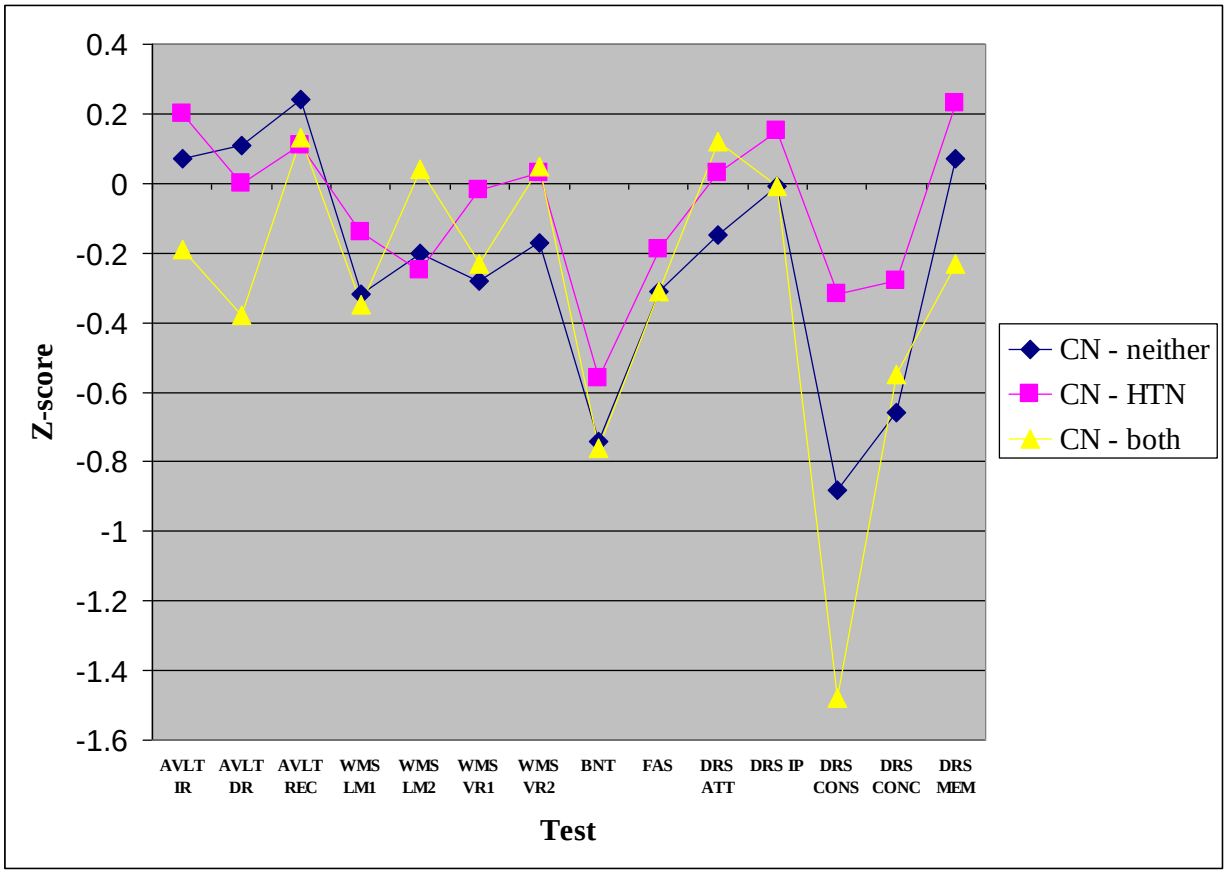
Note: AVLT = Rey Auditory Verbal Learning Test; IR = Immediate Recall; DR = Delayed Recall; WMS = Wechsler Memory Scale-Revised; LM = Logical Memory; VR = Visual Recognition; BNT = Boston Naming Test; COWAT = Controlled Oral Word Association Test; DRS = Mattis Dementia Rating Scale; ATT = Attention; IP = Initiation-Perseveration; CONS = Construction; CONC = Conceptualization; MEM = Memory; CN = Cognitively normal; HTN = Hypertension only; DM = Diabetes Mellitus only

Figure 2. *Profile analysis – AD sample*



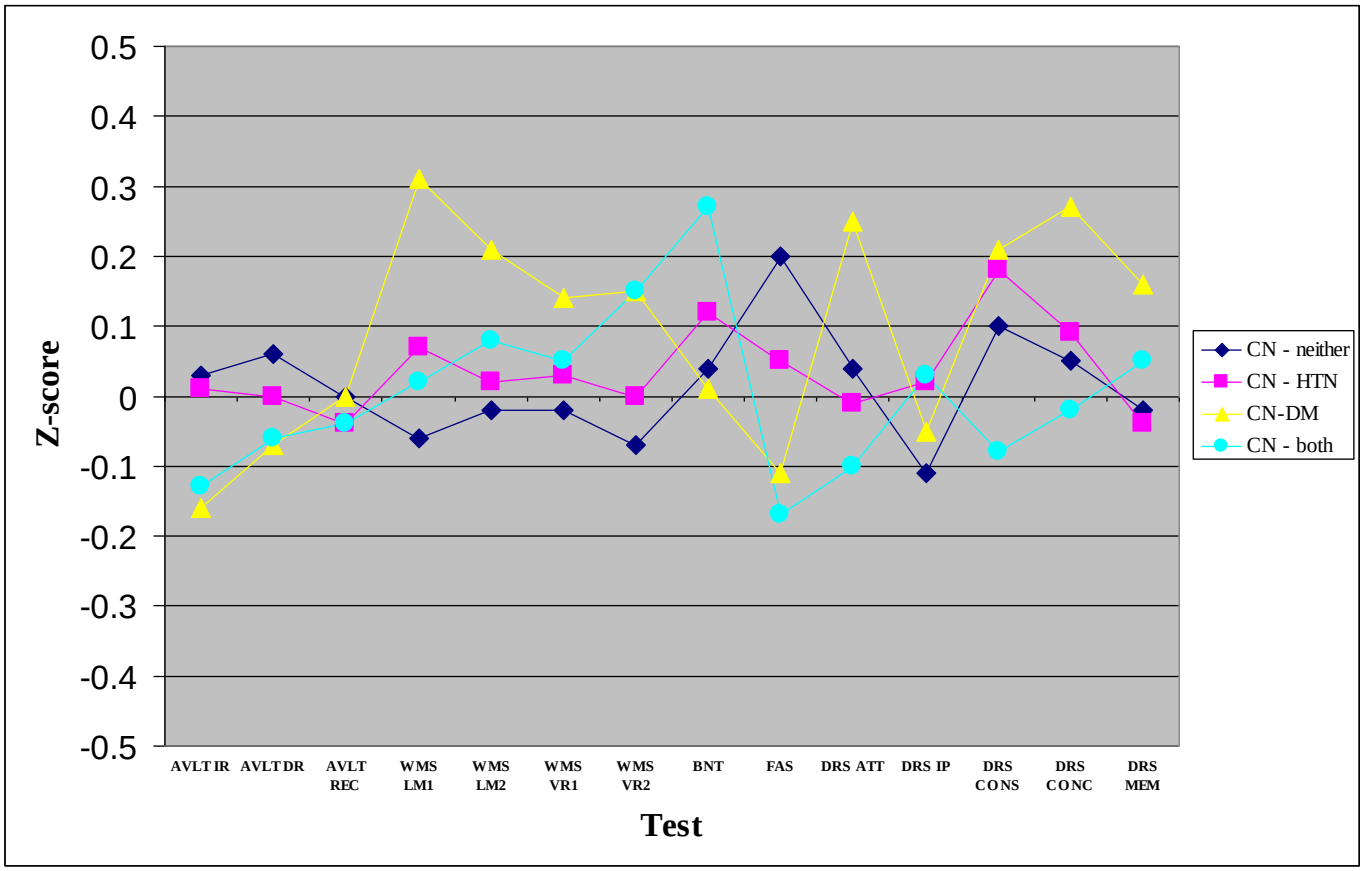
Note: AVLT = Rey Auditory Verbal Learning Test; IR = Immediate Recall; DR = Delayed Recall; WMS = Wechsler Memory Scale-Revised; LM = Logical Memory; VR = Visual Recognition; BNT = Boston Naming Test; COWAT = Controlled Oral Word Association Test; DRS = Mattis Dementia Rating Scale; ATT = Attention; IP = Initiation-Perseveration; CONS = Construction; CONC = Conceptualization; MEM = Memory; AD = Alzheimer's Disease; HTN = Hypertension only; DM = Diabetes Mellitus only

Figure 3. *Profile analysis – Cognitively normal African American sample*



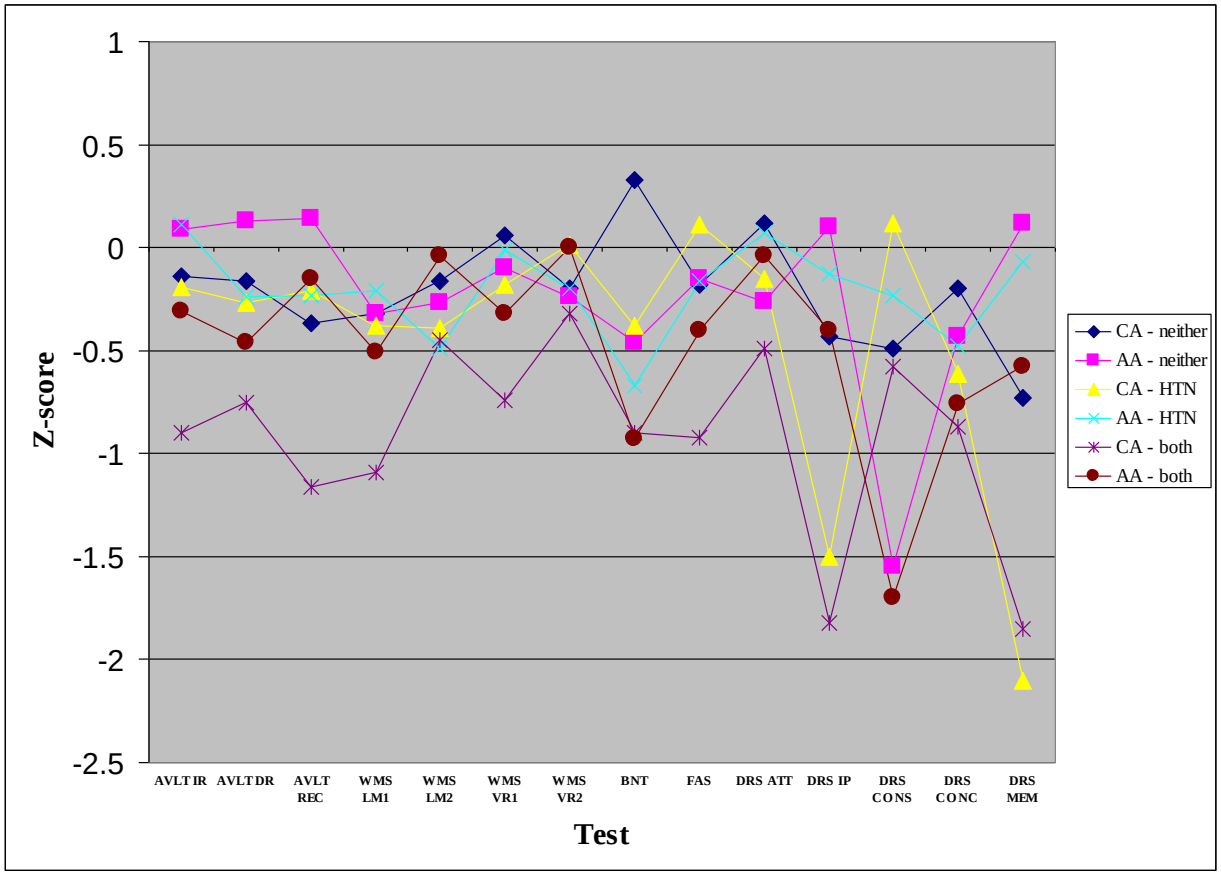
Note: AVLT = Rey Auditory Verbal Learning Test; IR = Immediate Recall; DR = Delayed Recall; WMS = Wechsler Memory Scale-Revised; LM = Logical Memory; VR = Visual Recognition; BNT = Boston Naming Test; COWAT = Controlled Oral Word Association Test; DRS = Mattis Dementia Rating Scale; ATT = Attention; IP = Initiation-Perseveration; CONS = Construction; CONC = Conceptualization; MEM = Memory; CN = Cognitively normal; HTN = Hypertension only

Figure 4. *Profile analysis – Cognitively normal Caucasian sample*



Note: AVLT = Rey Auditory Verbal Learning Test; IR = Immediate Recall; DR = Delayed Recall; WMS = Wechsler Memory Scale-Revised; LM = Logical Memory; VR = Visual Recognition; BNT = Boston Naming Test; COWAT = Controlled Oral Word Association Test; DRS = Mattis Dementia Rating Scale; ATT = Attention; IP = Initiation-Perseveration; CONS = Construction; CONC = Conceptualization; MEM = Memory; CN = Cognitively normal; HTN = Hypertension only; DM = Diabetes Mellitus only

Figure 5. *Profile analysis – Effects of both race and disease status on profiles among cognitively normal individuals*



Note: AVLT = Rey Auditory Verbal Learning Test; IR = Immediate Recall; DR = Delayed Recall; WMS = Wechsler Memory Scale-Revised; LM = Logical Memory; VR = Visual Recognition; BNT = Boston Naming Test; COWAT = Controlled Oral Word Association Test; DRS = Mattis Dementia Rating Scale; ATT = Attention; IP = Initiation-Perseveration; CONS = Construction; CONC = Conceptualization; MEM = Memory; CA = Caucasion; AA = African American; HTN = Hypertension only

CHAPTER IV

DISCUSSION

Findings

These results do not support the stated hypotheses. While analyses did indicate significant differences in profiles between disease groups for individuals with AD as well as between disease groups and ethnicities for normal individuals, the effect size in both analyses was below 10%. Furthermore, post-hoc tests revealed no significant effects of disease group on the individual cognitive tests. These findings suggest that overall group profiles, contrary to expected results, do not reveal significant and meaningful differences due to hypertension and diabetes.

Several factors may account for the lack of a significant impact of these medical conditions on the overall neurocognitive profiles of the current sample. First, the potential impact of medication status (i.e., controlled or uncontrolled hypertension and diabetes) was not assessed. Studies have suggested that cognitive performance among individuals taking anti-hypertensive medications does not differ from, and may in fact be better than, control participants without hypertension (Fischer et al., 2006; Insel et al., 2005). Furthermore, the use of anti-hypertensive medications has been linked to a decreased risk of cognitive impairment and Alzheimer's disease (Khachaturian et al., 2006). Similarly, the use of medication appears to protect against cognitive decline among individuals with diabetes. One study found that the use of ACE inhibitors and angiotensin receptor blockers (ARBs) was associated with less cognitive decline in a 1.5 year period among diabetic patients (Bruce et al., 2008). Effective diabetes treatment has further been associated with decreased Azheimer's-related neuropathology. Beeri et al.

(2008) found significantly lower numbers of neuritic plaques in the brains of diabetic individuals who had taken both insulin and oral antidiabetic medications during life compared to those who taken only insulin, only oral medication, or neither. The current study did not control for the use of anti-hypertensive or anti-diabetic medications, and it is highly possible that several individuals were on such medications, thus skewing results.

Second, insignificant findings may be related to statistical limitations. For example, the random deletion of cases to correct for homogeneity of variance-covariance may have lead to insufficient power for detecting significant differences. Insufficient power was obvious in a few of the analyses (i.e., observed power of 0.12 for the main effect of disease group on cognitive profiles in the cognitively normal sample), while other insignificant findings were associated with good to excellent power for detecting differences (i.e., observed power of 0.88 for the hypothesis of parallelism within the cognitively normal sample). Therefore, power issues do not likely account for the majority of the findings in the current study. Conversely, the Scheffe's correction used in post-hoc analysis is highly conservative, resulting in large critical F values, and thus may have lead to errant maintenance of the null hypotheses. Given that several post-hoc comparisons were close to significance, utilization of a more lenient approach to critical F values likely would have lead to some significant results. For example, the post-hoc one-way ANOVA examining group differences in AVLT-immediate recall within the Alzheimer's disease sample revealed a significant difference prior to Scheffe's correction and likely would have remained significant with a less conservative correction. However, the danger in selecting a more lenient correction lies in the possibility of inflating alpha levels and erroneously rejecting the null hypothesis.

Third, it is likely that differences in neuropsychological profiles do differ between groups but were not found using the current analyses. By simply examining figures 1-5, it becomes obvious that overall profiles do differ somewhat despite the fact that the current analyses did not reveal these differences to be significant. It is therefore probable that neuropsychological profiles do differ based on hypertension or diabetes status and were simply masked by the insensitivity of the analytic method. For example, the inclusion of all four groups (i.e., neither, hypertension only, diabetes only, and both) within the same profile analysis may have skewed any differences between specific groups. It is likely that the profiles of individuals with neither condition differ significantly from those of individuals with both conditions; however, inclusion of the additional two groups and thus additional variance may have masked these differences. Furthermore, the use of numerous dependent measures likely contributed to the lack of sensitivity for finding profile differences. In addition, the measures used, particularly the Dementia Rating Scale (DRS), may not have been sensitive enough to detect differences within the control group. The DRS was developed to examine cognitive functioning among individuals with suspected or known cognitive impairment and is thus insensitive to variances in normal cognition. The restricted range of variance of DRS subtest scores within the cognitively normal group thus decreased the power to detect any significant differences. Future studies should include more sensitive measures of the normal range of cognitive functioning.

Finally, the method of classifying and analyzing the presence or absence of diabetes and hypertension in this study likely impacted the results. As described previously, the presence of diabetes and hypertension was determined based upon either

a) self-report of diabetes or hypertension diagnosis, or b) the presence of diabetes- or hypertension-related diagnosis in medical records. The use of self-report and/or archival data versus objective measurement can introduce error variance into the analysis. For instance, individuals who divulge disease-related information often differ in systematic ways from individuals who are unwilling to reveal disease-status via self-report. Shah and Manuel (2008) found that only 75% of individuals with a physician diagnosis of diabetes reported this diagnosis. Furthermore, diabetic individuals who did not report the diagnosis engaged in less self-monitoring of blood glucose and ongoing physician care than those who did report a diagnosis of diabetes. Previous research using self-report and archival data versus studies using objective assessment methods has provided some discrepant findings. Desmond, Tatemichi, Palk, and Stern (1993) examined the relationship between self-reported hypertension and diabetes and cognitive functioning. Results revealed no relationship between hypertension and any of the cognitive domains studied; diabetes was related only to abstract reasoning and visuospatial abilities. Studies that have employed objective measures of blood pressure and glucose control, on the other hand, have found significant effects of these conditions on cognitive functioning (see Waldstein, 2003 and Awad, Gagnon, & Messier, 2004, for reviews). In addition, the use of categorical data (i.e., presence or absence of hypertension) did not allow for the examination of dose-effects on cognitive scores. The incorporation of continuous data provided by objective assessment methods, such as blood pressure readings or hemoglobin A1c measurements (a marker of glucose control), may allow for the investigation of additional effects, such as whether cognitive profiles differ between individuals with mild hypertension versus those with chronic and severe hypertension.

Furthermore, fluctuations in diabetics' blood glucose levels may lead to variable levels of cognitive functioning throughout the day. In a recent study, researchers examined subjects' fasting glucose levels before and after cognitive testing (Galanina, Surampudi, Ciltea, Singh, & Perlmuter, 2008). Results indicated that individuals in whom glucose levels decreased from pre- to post-testing performed significantly better on cognitive testing than those who demonstrated increases in glucose levels. Thus, fluctuations in glucose levels even over the course of neuropsychological testing may affect a patient's performance. This and similar studies suggest that objective measures of blood glucose and blood pressure at the time of testing may provide for a more accurate measurement of the effects of diabetes and hypertension on cognition.

Of course, it is possible that the lack of findings reflect the true state of the population. Overall neuropsychological profiles may indeed not differ between groups based on hypertension and/or diabetes status. These findings suggest that hypertension and diabetes are not necessarily associated with a singular cognitive profile, such as that commonly found among individuals with certain dementing disorders. Clinicians may not reliably assume that a certain pattern of scores is reflective of either condition. It is possible, however, that the cognitive profile of an individual patient will reflect changes due to hypertension and/or diabetes when individual test scores are examined. Clinicians must then take possible effects of hypertension and/or diabetes into account when interpreting individual test scores. Subtle impairments in cognitive domains such as immediate and delayed verbal memory may reflect information processing deficits associated with diabetes rather than a dementing syndrome per se. On the other hand, the deficits associated with hypertension and diabetes may reflect organic changes that can

lead to the onset of cognitive impairment severe enough to warrant a dementia diagnosis. Last et al. (2007) demonstrated an association between type 2 diabetes and decreased gray and white matter volumes as well as decreased cerebral perfusion. Hypertension is similarly associated with organic brain changes, including decreased cerebral perfusion (Efimova, Efimova, Triss, & Lishmanov, 2008), lacunar strokes (Fisher, 1982), and white matter lesions (see review by Tzourio, 2007).

The research and overall knowledge-base implications of the lack of findings are less clear. They may help explain why some studies (Nilsson et al., 1998) have found no differences between groups on measures of overall cognitive functioning, such as the MMSE. These findings, in conjunction with earlier studies that have found differences on individual tests, may also suggest that diabetes and hypertension effect specific cognitive domains rather than global cognitive functioning. In addition, it is likely that the effects of hypertension and diabetes on cognitive function differ based on several factors, such as medication use, structure of the task, and glucose control. Future research should attempt to determine third factors that influence this relationship. Hypertension and diabetes do not appear to be associated with a uniform, specific profile. Factors that determine if and in what domain an individual with hypertension and/or diabetes demonstrates cognitive impairment need to be illuminated. Discovery of moderating factors will likely provide avenues for prevention of cognitive impairment among sufferers of these diseases.

Despite the lack of significant findings in the profile analyses, follow-up regression analyses did suggest that while the presence of hypertension and diabetes may not lead significant group differences in overall cognitive profiles, these conditions do

appear to have some effects on individual cognitive scores, both in nondemented and demented individuals. It should be noted, however, that the majority of these effects did not hold up under Bonferroni correction for alpha level.

The mixed results demonstrated by follow-up analyses in the present study are similar to those of prior studies of the effects of hypertension and diabetes on cognitive functioning. Numerous former studies have revealed significant differences between individuals with hypertension and those without on verbal and visual memory tests (Elias et al., 1995; Elias et al., 1997; Elias et al., 2003; Saxby et al., 2003; Singh-Manoux & Marmot, 2005; Waldstein et al., 2001). Other studies have found no such association (Glynn et al., 1999; Kuo et al., 2005). The effects of hypertension on memory in the present study were not significant, although there was a trend toward significance when predicting memory for stories and visual stimuli. Discrepant findings in the literature as well as the current study likely reflect methodological differences, which include the method of defining hypertension in addition to variable statistical methods.

Hypertension was significantly predictive of higher scores on tasks of confrontational naming, an effect that has not been shown in previous studies. Reitz et al. (2007) found no difference between hypertensives and nonhypertensives on the BNT. Interestingly, the effect of hypertension on confrontational naming scores was not seen once the cognitively normal sample was divided by ethnicity. Scores on BNT were not significantly affected by hypertension in Caucasians or African Americans.

The effects of hypertension on cognitive performance differed in other ways when subjects were divided by ethnicity. Among Caucasians, hypertension was not associated with performance on any of the cognitive measures. Conversely, hypertension was

predictive of higher scores on visual reproduction among African Americans. This finding is at odds with much of the current literature which tends to show a decrease in visual reproduction scores among individuals with hypertension or higher systolic blood pressure (Elias et al., 1995; Elias et al., 2003; Waldstein et al., 2001). Bohannon et al. (2002) found no significant relationship between systolic blood pressure and cognitive decline, an effect that was seen in the study's Caucasian sample. Hebert et al. (2004) similarly found a greater decline among Caucasians with higher diastolic blood pressure than among African Americans with similarly high diastolic blood pressure. Unlike the greater impact of hypertension and/or high blood pressure on cognitive functioning among African Americans as seen in other studies (Robbins et al., 2005), the findings of Hebert et al. (2004) provide evidence that the impact is actually greater in Caucasians. The current study suggests that there may be a greater impact on cognition among African Americans in which those with hypertension perform better on visual reproduction tasks than those without, although this finding was only marginally significant at the $p < .05$ level and therefore should be interpreted with caution. Reasons for this particular finding are unclear, particularly given that African Americans tend to have lower levels of blood pressure control than Caucasians. It is possible, however, that the African Americans within this specific sample were more likely to be taking antihypertensive medications. It is also possible that African-American subjects in the non-hypertensive group had low blood pressure, affecting their cognitive performance. Wharton et al. (2006) demonstrated that low blood pressure is associated with poorer performance on visual attention tasks among healthy individuals. Given the importance of attention in encoding of visual information, it is possible that subjects with lower

blood pressure in the current study performed worse on visual memory tasks due to poor attention to initial presentation of stimuli. Thus, subjects with higher blood pressure, such as those in the hypertensive group, may have had a slight advantage on this particular task.

As stated earlier, the use of antihypertensive medications likely served as a confounding variable in the present study, possibly accounting for differences between current findings among cognitively normal individuals and those of earlier studies. It is also possible that U-shaped relationship between blood pressure and cognition often seen in similar studies (Bohannon et al., 2002; Glynn et al., 1999) affected the current results. This study did not examine the effects of low systolic or diastolic blood pressure. Conceivably, some of the subjects within the CN-neither or CN-DM only group were hypotensive. This hypotension may have affected their cognitive performance and thus distorted results. Future studies may correct for this by utilizing continuous data via objective measurements of blood pressure.

Regression analyses revealed a significant effect of diabetes on list learning and visuoconstructional tasks among cognitively normal individuals, which the alpha level was maintained at 0.05. These results are partially congruent with those of Arvanitakis et al. (2004), who found lower scores on episodic memory and visuospatial abilities among individuals with diabetes, in addition to working and semantic memory, both of which were not specifically tested in the present study. Furthermore, the effect of diabetes on verbal memory has been found in several other studies (Kuo et al., 2005; Pearlmuter et al., 1984; Reaven, Thompson, Nahum, & Haskins,1990; U'ren et al., 1990; Verhaeghen, Borchelt, & Smith, 2003). Contrary to some studies, however, diabetes in the current

sample was only related to list learning and not story memory. Cosway, Strachan, Dougall, Frier, and Deary (2001) found similar results. Conversely, cognitive domains found to be affected by diabetes in previous studies were not significantly related to diabetes in the present study. For example, Desmond et al. (1993) found a significant effect of diabetes on abstract reasoning. A similar measure in the present sample, DRS Conceptualization, was not affected by the presence of diabetes among cognitively normal individuals.

The effects of diabetes on cognition differed by ethnicity within the cognitively normal group. Among Caucasians, diabetes was associated with lower scores on verbal memory, verbal fluency, and visuoconstruction. Conversely, there were no significant effects of diabetes on any cognitive domains among African Americans, although there was a significant trend towards an effect on visuoconstruction. Although the differential effects of diabetes on cognitive functioning between Caucasians and African Americans have not been extensively studied, a recent study revealed lower cognitive performance for African Americans with diabetes than Caucasians with diabetes (Obidi et al., 2008). This finding is unsurprising given evidence that African Americans with diabetes tend to have lower glycemic control than Caucasians, possibly as a result of differences in socioeconomic status and/or medication adherence (Heisler et al., 2007). The current findings, conversely, suggest that the presence of diabetes may be more significantly associated with cognition among Caucasians than African Americans. However, the effects of diabetes on cognition among Caucasians were not found when the more conservative alpha level was applied via Bonferroni correction. These findings, thus, may have reflected increased Type I error due to multiple comparisons. Furthermore,

while there were no significant findings among African Americans, the partial correlations of diabetes with performance on several cognitive tasks were comparable to those of Caucasians. It is also therefore likely that the extremely low number of African Americans with diabetes in the current sample resulted in too little power to detect a significant effect.

Regression equations within the AD group revealed a significant effect of hypertension on lower verbal fluency and executive functioning (i.e., DRS Initiation-Perseveration) scores as well as higher delayed visual recall scores. Goldstein et al. (2005) found a similar effect of hypertension on Initiation-Perseveration scores, in addition to Conceptualization scores, within a sample of AD patients, an effect not seen in the present sample. One potential explanation for the effects of hypertension on cognitive performance among AD patients is found in the findings of Petrovich et al. (2000). Results showed significantly higher levels of neurofibrillary tangles within the hippocampus and neocortex, a neuropathological hallmark of AD, within the brains of individuals with the highest systolic and diastolic blood pressure levels in midlife. In addition, these pathological changes within the hippocampus were more pronounced in individuals with lower systolic blood pressure in midlife. Thus, the influence of hypertension on the cognitive performance of patients with AD may reflect an increase in the amount of AD pathology within the brain. On the other hand, the present study found higher delayed visual recall scores among AD patients with hypertension. The reason for this particular finding is unclear. However, one factor that may have contributed to differential findings between the present study and earlier literature is the use of anti-hypertensive medications as described previously.

Also among individuals with AD, the presence of diabetes was shown to be significantly predictive of lower performance on a measure of attention and higher performance on a general measure of memory. The effects of diabetes within AD patients have not been fully explored previously and thus reasons for these findings are unclear. It is possible that increased impairment on attention is associated with diabetes itself, as attention has been found to be impaired in nondemented individuals with diabetes relative to controls (Dey, Misra, Desai, Mahapatra, & Padma, 1997). Conversely, diabetes may increase the risk for vascular pathology, including infarctions and white matter disease, within individuals with AD, thus adding to the cognitive impairment resulting from AD-related brain changes. In a study by Biessels, De Leeuw, Lindeboom, Barkhof, and Scheltens (2006), individuals with AD and type 2 diabetes had increased cortical atrophy relative to AD patients without diabetes. In addition, infarctions were more prevalent in the AD group with diabetes than in those without, although this finding was not significant. Reasons for higher performance in memory among individuals with diabetes are even more unclear. Among cognitively normal individuals, those with diabetes have been shown to perform worse on memory tasks in the majority of past studies (Arvanitakis et al, 2004; Debling et al., 2006; Dey et al., 1997; Elias et al., 1997; Hassing et al., 2003; Van Harten et al., 2007; Verhaeghan et al., 2003; Wahlin, Nilsson, & Fastbom, 2002), while other studies have found no difference in memory performance based on diabetes status (Cosway et al., 2001; Reitz et al., 2007; Ryan & Geckle, 2000). All of these studies, however, were conducted with cognitively normal individuals. Possible reasons that AD subjects in the present study with diabetes performed better than those without diabetes include the use of insulin and other diabetes

medication, the use of which has recently been shown to be associated with decreased neuritic plaques – a hallmark of AD – within the brains of diabetic individuals (Beeri et al., 2008). Perhaps individuals with diabetes and AD in the present study were on diabetes medications and thus had decreased AD pathology, resulting in slower decline of memory performance. Again, however, these findings, as well as those regarding the effects of hypertension on cognitive scores in AD patients described above, must be interpreted with caution given the fact that the majority of these effects were no longer significant at the $p < 0.004$ level of the Bonferroni correction, and thus may represent inflated Type I error.

Implications

The present findings do not support the hypothesis that individuals with hypertension and/or diabetes have differing overall cognitive profiles to those without. On the other hand, results do suggest that the presence of hypertension and/or diabetes does affect performance on specific cognitive measurements in both cognitively normal individuals and those with AD. Furthermore, these effects differed between Caucasians and African Americans within the cognitively normal sample.

Overall, these findings provide neuropsychologists and related practitioners with knowledge regarding expected cognitive functioning of individuals with hypertension and/or diabetes. Neuropsychologists, particularly those in medical settings, often find themselves presented with patients that have numerous health problems, frequently including the two conditions currently of interest. Often these practitioners are forced to tease apart the effects of medical conditions on cognition from those of organic brain

dysfunction (i.e., dementia, traumatic brain injury, tumor). The present results and those of similar studies provide neuropsychologists with a basis for determining a proper diagnosis. In addition, other health care professionals, including medical doctors, psychologists, and social workers, can use this knowledge to inform care planning for individuals with hypertension or diabetes. For example, cognitively normal individuals with diabetes may have subclinical deficits in verbal memory and thus may need assistance in setting up strategies for remembering to take their medications.

In addition to clinical applications, the present results will hopefully inform future research studies. A knowledge of which cognitive domains are most affected by hypertension and diabetes can provide evidence for the specific brain regions most influenced by vascular and/or chemical changes characteristic of these conditions. Results of this and similar studies may also inform studies examining the risk of dementia among individuals with hypertension and diabetes. Perhaps the cognitive deficits associated with hypertension and diabetes represent components of a prodromal stage of dementia. Similarly, perhaps increased control of hypertension and diabetes will decrease cognitive impairment and/or subsequent development of dementia.

Limitations and proposed future research

The current study has several limitations. First, sample characteristics and recruiting methods limit generalizability of findings. While a large number of individuals are contacted to participate in studies within the Mayo Clinic, a smaller number actually choose to participate. Data are not available comparing those individuals who do and do not choose to participate, but one can consider several characteristics that may

differentiate these two groups and thus limit generalizability. For example, education levels may be lower among individuals who choose not to participate due to a lack of knowledge regarding scientific study and methods. It is further possible that individuals choosing not to participate were more likely to have uncontrolled medical conditions, such as hypertension or diabetes, that limited their abilities to engage in extensive neuropsychological testing. Furthermore, nonparticipants may harbor a distrust of research and the medical profession in general. Past mistreatment of subjects, particularly of African Americans, has likely left distaste for medical research among these populations. Those who chose to participate were likely more trusting of the research process and thus more willing to cooperate with testing.

A second sample characteristic that potentially limits generalizability of the present findings is regional location. First, subjects were recruited and tested in either Rochester, Minnesota, or Jacksonville, Florida. Regional differences in educational quality, diet, vernacular, socioeconomic status, etc., likely influenced subject's performance. Furthermore, the majority of African Americans were tested in Jacksonville, while the majority of the Caucasians in the present sample were tested in Rochester. Thus, factors related to regional differences may account for differences between the ethnic groups rather than the factor of ethnicity itself. Future research should examine similar factors in other populations, such as individuals with vascular dementia, Hispanic Americans, or individuals in other regions of the country, in order to increase generalizability.

The methods through which data on hypertension and diabetes were obtained limit both the generalizability and possibly the interpretation of these results. In the

present study, a subject was considered to have hypertension and/or diabetes if 1) they indicated a history of either condition through self-report or 2) review of medical records revealed related diagnoses. Self-report data are a limitation to any study, as they are subject to any number of biasing factors, including demand characteristics or a desire to minimize one's deficits. Furthermore, it is possible that many of the subjects in the present study were suffering from hypertension- or diabetes-related conditions but were unaware of the situation. Review of past medical records can also introduce error, thus skewing results. In the present study, a subject was considered to be positive for hypertension and/or diabetes if he or she had any related condition in his or her records. These conditions included borderline blood pressure and hyperglycemia, both subclinical versions of and/or precursors to the diseases of interest. Furthermore, it is likely that reviewed medical records were incomplete; thus, diagnoses dating back several years or those made at other facilities and not subsequently reported may have gone unnoticed. This and future studies would be improved with the use of objective measures of hypertension and diabetes, such as blood pressure and glucose level readings.

Hypertension and diabetes are rarely seen in isolation. Frequent comorbidities include obesity, atherosclerosis, stroke, metabolic syndrome, and heart disease. These conditions were not controlled for in the current study (with the exception of stroke) and thus could have skewed results. Perhaps these other conditions accounted for differences in cognitive performance. In addition, individuals with hypertension and diabetes are frequently on medications to control symptoms. The effects of hypertension and diabetes on cognitive function are related to the amount of control on blood pressure and blood glucose (Fischer et al., 2006; Reaven et al., 1990); however, the use of medication was

not accounted for in the present study. Future studies should control for comorbidities as well as the use of medication.

In addition, it is likely that several individuals within the "cognitively normal" group were actually in a prodromal stage prior to onset of mild cognitive impairment or dementia. While the criteria required for a diagnosis of AD or similar dementia were not met at the time of testing, decreased cognition may have already been evident on neuropsychological testing, the results of which were not used when making a diagnosis. These individuals may have developed clinically-relevant cognitive impairment within two or three years of participation in the current study. Similarly, individuals in the AD group were likely at different stages of dementia (i.e., mild versus moderate). Dementia staging data was not available in the present study but likely contributed to the current findings. It is possible that individuals with hypertension were at a more moderate or severe stage of dementia at time of testing than those without hypertension, and thus, findings of the effect of hypertension on cognitive performance within demented individual were actually the result of dementia stage rather than hypertension itself. In order to control for these factors, future research should take dementia severity into account.

Education was controlled for in each performed analysis. Thus, all significant effects were seen over and above the effects of education. However, previous research has suggested that years of education may not be the best marker of educational attainment given the discrepancies in quality of education between regions or even between schools within the same city (O'Bryant, Schrimsher, & O'Jile, 2005). Other studies have recommended the use of reading ability as a marker of education (Manly et

al., 2002; Manly et al., 2004). A measure of reading level was not available for all participants in the current study and thus years of education were utilized. It is possible that individuals in the current sample with identical amounts of education were actually exposed to very different educational quality. Consequently, had reading ability been controlled for, the impact of diabetes and hypertension on cognitive performance may have changed. Future studies should include a more accurate measure of educational quality to better control for educational effects.

Finally, future research should examine longitudinal effects of hypertension and diabetes on cognitive profiles. The cross-sectional nature of the current study limits conclusions on causal mechanisms. Future research should answer the question of whether the presence of hypertension and diabetes at one time predicts different overall profiles at a future time.

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APPENDIX A.

Expanded Literature Review

Because AD remains at present an incurable disease, researchers have attempted to pinpoint risk factors that may provide opportunities for modification, treatment, or disease prevention. As early as 1931, researchers began to realize that AD was a disease with a myriad of possible etiologies and factors associated with its development (Lowenberg & Rothschild, 1931). In 1968, Blessed, Tomlinson, and Roth stated that "there is no causal relationship between the processes responsible for plaque formation and cerebrovascular disease" (p. 802). However, researchers now suggest that AD lesions are the result of vascular changes in the brain. Recently, researchers have focused on the potential for cardiovascular risk factors to increase the risk for AD (for reviews, see Breteler, 2000, de la Torre, 2002, and Stampfer, 2006). Factors that have been implicated in the risk for AD include hypertension, diabetes mellitus, obesity, arteriosclerosis, and smoking. The aim of the following review is to examine the literature regarding increased risk for AD associated with cardiovascular risk factors as well as proposed biological mechanisms underlying these relationships.

Hypertension and elevated blood pressure

In a study of 3703 Japanese-American men in Hawaii, Launer et al. (2000) found that a significantly increased risk for all dementias was associated with high and low diastolic blood pressure (DBP) as well as high systolic blood pressure (SBP). Controlling for age, education, ApoE allele status, smoking, and alcohol consumption, the odds ratio of dementia associated with borderline high DBP (between 90 and 94 mmHg) was 3.8

(95% confidence interval: 1.6-8.7), while that associated with DBP of 95 mmHg or higher was 4.3 (1.7-10.8). Untreated SBP of 160 mmHg or higher was associated with an odds ratio for dementia of 4.8 (2.0-11.8). Kivipelto et al. (2005) reported similar increased risk of AD associated with higher SBP in midlife.

Another group of studies have suggested that low blood pressure is associated with increased prevalence of AD. In the Chicago Health and Aging Project, the prevalence of AD was significantly higher among individuals with SBP of less than 130 compared with individuals with higher SBPs of 130 to 139 (Morris et al., 2000). High SBP of 160 or greater was only associated with increased AD risk in a subsample of individuals with heart disease, stroke, or diabetes. Gou et al. (1997) reported an association between poor cognitive functioning and lower systolic (less than 130) or diastolic (less than 75) blood pressure at baseline. However, high systolic (greater than or equal to 180) or diastolic (greater than or equal to 95) blood pressure at baseline was associated with significantly increased risk of cognitive decline at follow-up. Hebert et al. (2004) demonstrated a U-shaped relationship between DBP and decline in cognitive function, with both higher and lower DBP scores showing an association with greater decline at follow-up.

Other studies have reported no significant association between hypertension and dementia risk (Lindsay et al., 2002; Posner et al., 2002; Prince, Cullen, & Mann, 1994). According to a study by Luchsinger et al. (2005), hypertension was related to a higher risk of AD when considered alone; however, when hypertension, diabetes, heart disease, and current smoking were entered into the same model predicting AD, the effects of hypertension were no longer significant. Landin, Blennow, Wallin, and Gottfries (1993)

reported lower SBP and DBP in AD patients compared to patients with other dementing disorders, specifically vascular dementia and nonspecificed dementia. A further group of studies suggests that hypotension, particularly diastolic hypotension, in individuals over 75 is associated with increased risk of AD, possibly resulting from cerebral hypoperfusion or as a consequence of vascular and neurotransmitter changes within the brains of AD patients (Verghese, Lipton, Hall, Kuslansky, & Katz, 2003). Qiu, von Strauss, Winblad, and Fratiglioni (2004) found a significant decrease in systolic blood pressure beginning three years prior to dementia diagnosis, with greater declines predicting development of dementia in individuals with a history of low blood pressure.

Overall, these results suggest that the nature of the relationship between hypertension and/or elevated blood pressure and dementia, particularly AD, remains unclear. Both high and low blood pressures have been shown to be associated and not associated with increased risk for cognitive decline or dementia. Differences in assessment methods for hypertension (e.g. self report versus clinical assessment of blood pressure), sample characteristics (e.g. community versus clinical settings), or outcome measures (e.g. various criteria used to define dementia or AD) may at least partially account for discrepant findings. Because hypertension is a preventable risk factor, however, the illumination of its relationship with dementia or AD would have important clinical applications for the prevention of cognitive impairment.

Blood pressure has been associated with increased numbers of characteristic AD lesions. In a study by Petrovitch et al. (2000), the presence of AD-associated lesions (i.e., neurofibrillary tangles and neuritic plaques) at autopsy were examined in relation to blood pressure at midlife. The authors found that the highest numbers of both lesion

types were found among patients with the highest and lowest levels of SBP at midlife. Furthermore, a higher number of neuritic plaques in the hippocampus was found among individuals with high midlife-SBP; a higher number of neurofibrillary tangles in the hippocampus was found among individuals with high midlife DBP. The presence of AD lesions did not appear to be related to the presence of cerebrovascular lesions, thus suggesting that hypertension contributed directly to the accumulation of AD neuropathology. Inversely, there remains the possibility that neuropathological changes associated with AD increase the risk of hypertension. A review by Farkas, De Vos, Steur, and Luiten (2000) discussed findings of decreased cerebral perfusion among individuals with AD as well as the vasoconstrictive effects of β-amyloid found in amyloid plaques. Both factors contribute to restricted blood flow to the brain and thus may result in increased blood pressure to compensate for these changes. Despite this possiblility, Landin et al. (1993) found that AD patients had lower blood pressure than control participants, providing evidence against this hypothesis.

Several biological mechanisms have been proposed to explain a possible relationship between hypertension and increased risk of AD. One hypothesis has been that high or low blood pressure contributes to the accumulation of AD lesions via chronic hypoperfusion, or lowered cerebral blood flow. Decreased cerebral blood flow in the hippocampus and neocortex is characteristic of AD (Farkas et al., 2000), and hypertension has been shown to decrease cortical perfusion (Meyer et al., 2000). In their review, Farkas et al. (2000) suggest that a constant state of decreased cerebral blood flow results in a reduction of glucose and oxygen in the brain, both of which are needed for

optimal brain function and metabolism; the metabolism of both glucose and oxygen is reduced in AD.

Diabetes mellitus and insulin resistance

The relationship between diabetes mellitus and dementia, specifically AD, is somewhat controversial. Several studies have shown an increased prevalence of diabetes among patients with AD as compared to nondemented controls (Kuusisto et al., 1997; Leibson et al., 1997). Arvanitakis et al. (2004) reported a hazard ratio for AD associated with the presence of diabetes of 1.65 (1.10-2.47) among a population of Catholic nuns and priests. Peila, Rodriguez, and Launer (2002) found similar results after controlling for potential demographic and cardiovascular factors. In a systematic review of the literature, Biessels et al. (2006) found an overall 50% to 100% increased incidence of AD among individuals with diabetes compared to those without diabetes. Others have found no significant association between diabetes and increased AD risk (Curb et al., 1999; Lindsay et al., 2002) and many studies show a higher risk for vascular dementia rather than AD associated with diabetes (Ott et al., 1996; Xu et al., 2004). Furthermore, diabetes has been shown to be associated with cerebral infarcts, not increased AD neuropathology (Arvanitakis et al., 2006).

Even in the absence of diagnosed diabetes, high levels of insulin and glucose or glucose resistance have been associated with increased risk of dementia. The Washington Heights-Inwood Columbia Aging Project (WHICAP), a community study in Manhattan, New York, revealed a hazard ratio of AD associated with hyperinsulinemia or diabetes of 2.2 (1.6-3.2); 39% of the risk of AD could be attributed to hyperinsulinemia

or diabetes (Luchsinger, Tang, Shea, & Mayeux, 2004). Increased risk for AD in a study by Kuusisto et al. (1997) was associated with high fasting insulin levels, even among subjects without diabetes.

An overall review of the literature reveals a similar picture to that of hypertension. While some studies suggest a strong link between diabetes or insulin levels and AD risk, other findings oppose the existence of an association. Again, possible reasons for discordant findings in the literature include methodological differences, specifically differences in testing for glucose intolerance or the presence of diabetes. Furthermore, controlled factors vary by study; some studies controlled for several cardiovascular risk factors and demographics, while others controlled for only a few. Nevertheless, the proposed link between diabetes and AD is potentially one of immense clinical implications, possibly leading not only to preventative measures but the possibility of treatment.

Several reviews have explored possible biological mechanisms underlying the relationship between diabetes or high insulin levels and dementia risk (Biessels & Kappelle, 2005; Craft & Watson, 2004; Gold, 2005; Haan, 2006). One possible biological mechanism relating diabetes to AD is the formation of advanced glycation end products (AGEs) resulting from the break down of sugar, which have been associated with both conditions (Nicolls, 2004). The accumulation of AGEs is toxic to neurons (Biessels & Kappelle, 2005) and may contribute to the formation of amyloid plaques (Breteler, 2000). Recently, attention has been paid to the role of insulin-degrading enzyme (IDE) in the pathogenesis of AD. IDE has been shown to be involved in the degradation of Aβ, the principle component of amyloid plaques characteristic of AD, as

well as its clearance from the extracellular space in the brain (Morelli et al., 2004; Qiu & Folstein, 2006). Furthermore, IDE has been found to be decreased in the brains of AD patients (Morelli et al., 2004), particularly within the hippocampus (Biessels et al., 2006). Several authors have suggested that diabetes results in increased levels of insulin in the brain, which may lead to increased levels of Aβ in the brain (Biessels & Kappele, 2005; Craft & Wilson, 2004; Qiu & Folstein, 2006). Insulin not only appears to stimulate the release of Aβ in the brain, but also competes for IDE, thereby reducing the effectiveness of IDE in clearing Aβ from the brain. Aβ subsequently amalgamates within the brain parenchyma, resulting in the formation of amyloid plaques. In addition, a study by Freude et al. (2005) provides evidence of an effect of hyperinsulinemia on hyperphosphorylation of tau, the mechanism underlying the development of AD-hallmark neurofibrillary tangles (NFTs).

Atherosclerosis

While not as extensively studied as hypertension and diabetes, atherosclerosis within cerebral arteries has been implicated in AD. Beach et al. (2007) compared atherosclerosis within the circle of Willis in the brains of 215 patients with AD, 30 patients with vascular dementia, 60 with non-AD dementias, and 92 controls. Results indicated that while circle of Willis atherosclerosis was most common in vascular dementia cases, AD cases had significantly higher atherosclerosis scores than both the non-AD dementia and control groups. For each unit increase in the circle of Willis atherosclerosis grade, the odds ratio predicting AD risk was 1.31 (95% confidence interval = 1.04-1.69). Furthermore, circle of Willis atherosclerosis was associated with

markers of AD pathology (neuritic plaques and Braak stages). Similarly, Honig, Kukull, & Mayeux (2005) reported increased neuritic plaques associated with large-vessel atherosclerosis; the highest frequency of plaque counts was found among those with atherosclerosis. This association was stronger among individuals with dementia than those without dementia. In a study by Roher, Esh, Rahman, Kokjohn, and Beach (2004), the leptomeningeal arteries of 10 AD patients had "extensive" atherosclerosis and the severity of arterial stenosis was significantly correlated with the number of AD lesions. Results in another study revealed an increased risk of AD associated with increased intra-medial thickness of the common carotid artery (a marker of atherosclerosis; Van Oijen et al., 2007). Taken together, these results suggest a link between atherosclerosis of cerebral arteries and the development of AD neuropathology and dementia.

What might account for this proposed link? Casserly and Topol (2004) suggest that atherosclerosis is not directly associated with AD; rather, the two conditions result from independent but related disease processes, sharing risk factors, similar pathogenesis, and similar responses to treatment. Other authors have suggested a direct effect of atherosclerosis on the development of AD. In a discussion of their findings, Roher et al. (2004) hypothesize that atherosclerosis and other cerebrovascular abnormalities may lead to decreased cerebral blood flow, which has been implicated in AD pathogenesis.

Obesity

Studies examining obesity based on increased body mass index (BMI) have demonstrated a significant relationship with the risk of AD. Buchman, Schneider, Wilson, Bienias, and Bennett (2006) reported a significant correlation between increased

BMI and the number of AD lesions at autopsy - each unit increase in AD neuropathology was associated with approximately a one-unit increase in BMI among individuals with and without dementia prior to death. Furthermore, this relationship was significant even after controlling for chronic disease and physical activity during life. In that same cohort, each unit increase in BMI was associated with approximately a 5% greater risk for development of clinical AD (Buchman et al., 2005). Whitmer, Gunderson, Barrett-Connor, Quesenberry, and Yaffe (2005) reported a 74% increase in risk for dementia among individuals who were obese (BMI greater than or equal to 30) at midlife. Another study found that BMI among individuals who developed AD was 3.6 points higher than among individuals who remained nondemented (Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003). Elevated BMI has also been associated with poorer performance on cognitive measures (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2005; Kilander, Nyman, Boberg, & Lithell, 1997).

Obesity may contribute to inflammatory mechanisms in the brain, thus increasing the development of AD neuropathology. Jagust, Harvey, Mungas, and Haan (2005) noted that adipose tissue promotes the production of inflammatory cytokines which have been implicated in AD development. In their review, Cereda, Sansone, Meole, and Malavazos (2007) suggest that obesity is a risk factor for other diseases shown to be associated with AD risk, such as diabetes and hypertension; these other conditions may mediate the associated between obesity and AD. However, as mentioned previously, elevated BMI has been associated with AD pathology even after controlling for these other conditions (Buchman et al., 2005).

Interestingly, weight appears to decrease shortly before the onset of dementia in AD. Johnson, Wilkins, and Morris (2006) reported a significant weight loss one year prior to dementia onset among AD patients. In the Buchman et al. (2005) study, each one-unit loss of BMI per year was associated with about a 25% increase in the risk for AD compared with individuals whose BMIs did not change; an annual loss of one pound was associated with a 5% increase in AD risk. Johnson et al. (2006) suggested that decreases in weight prior to dementia onset may be related to changes in metabolism in the brains of individuals who developed AD.

Metabolic syndrome

The metabolic syndrome is a condition incorporating several cardiovascular risk factors (International Diabetes Federation, 2006). According to criteria established by the International Diabetes Federation (2006), the diagnosis of metabolic syndrome includes the presence of central obesity, as measured by waist circumference, along with the presence of two of the following: elevated triglycerides (150 mg/dL or greater) or treatment for elevated triglycerides; decreased high-density lipoprotein (HDL) cholesterol (less than 40 mg/dL in men, less than 50 mg/dL in women) or treatment for reduced HDL; elevated blood pressure (SBP greater than or equal to 130 mmHg or DBP greater than or equal to 88 mmHg) or treatment for diagnosed hypertension; and increased fasting plasma glucose (FPG; 100 mg/dL or greater) or diagnosis of type 2 diabetes.

The metabolic syndrome as an entity is a relatively new concept; therefore, research on its association with AD risk is scarce. Most studies have examined the

individual components of metabolic syndrome in relation to AD rather than the syndrome as a whole. Among studies that have specifically examined the condition, metabolic syndrome appears to be more prevalent among individuals with AD, particularly in women (Vanhanen et al., 2006). Razay, Vreugdenhil, & Wilcock (2007) reported that the risk of AD among individuals with the metabolic syndrome was more than three times that of individuals without the metabolic syndrome.

The relationship between metabolic syndrome and risk for AD can likely be attributed to the syndrome components. This review has provided evidence for an association between all components of the metabolic syndrome and AD. For instance, hypertension likely leads to decreased cerebral blood flow, providing a ripe environment for the development of AD pathology. Furthermore, insulin, as presented above, likely contributes to Aβ formation and accumulation of amyloid plaques. Thus, the metabolic syndrome may relate to AD via its individual parts rather than as an entity in and of itself.

Cigarette smoking

Current cigarette use has been associated with an increased risk for AD (Juan et al., 2004; Luchsinger et al., 2005). A history of cigarette smoking is associated with increased cerebral atrophy, which is marked among individuals with clinical AD (Meyer et al., 2000). However, there are also inconsistent findings. Sabbagh et al. (2005) found no association between smoking and cognitive decline. Leibovici, Ritchie, Ledesert, and Touchon (1999) reported similar results, with no significant risk of AD or AD neuropathology attributed to smoking after controlling for age and education. Tyas et al. (2003) reported a higher proportion of smokers among individuals with AD; however, the

association between AD and smoking was no longer significant when examining only those with the highest level of smoking.

A lack of association between smoking and AD seen in several studies may reflect higher mortality rates associated with chronic tobacco use. Wang, Fratiglioni, Frisoni, Viitanen, and Winblad (1999) reported an inverse relationship between AD and smoking: those with AD were less likely to be smokers than those without AD. In fact, several studies have demonstrated a protective effect of smoking on AD (Graves et al., 1991; Ott et al., 1998; Wang et al., 1997). However, Wang et al. (1999) also reported a significant association within the dementia group of smoking and mortality. Thus, it is likely that many individuals with AD with a history of smoking are not included in these studies because of increased morbidity and mortality. Furthermore, cigarette smokers may not live long enough to develop full-blown clinical AD.

Cigarette smoking likely contributes to AD risk via other risk factors, such as hypertension and heart disease. A review by Sabbagh, Lukas, Sparks, and Reid (2002) provides an overview of other possible biological mechanisms linking tobacco use as both a protective factor and risk factor for AD. Nicotine has been found to inhibit the accumulation of Aβ plaques by preventing the formation of β-sheets. Futhermore, nicotine use has been shown to increase acetylcholine activity, which is decreased in AD, at nicotinic receptors in brains of animals and humans. On the other hand, chronic exposure to high levels of nicotine results in a loss of nicotinic receptor sensitivity. In addition, loss of acetylcholine nicotinic receptors has been correlated with levels of Aβ in the brain. Thus, lower levels of nicotine use appear to be somewhat protective against the formation of Aβ plaques and loss of acetylcholine characteristic of AD; risk of AD

associated with cigarette smoking likely results from brain chemistry alterations due to chronic nicotine exposure among heavy smokers.

Proposed vascular mechanisms of AD

Several broad theories suggesting vascular mechanisms involved in AD have been postulated in the literature. Cullen, Kocsi, and Stone (2006) have suggested that microhemorrhages within the brain parenchyma contribute to the aggregation of Aβ into senile and neuritic plaques. The authors examined haem-rich deposits (HRDs), which form around small brain vessels and are a marker of intracerebral bleeding, in the brains of individuals with and without AD. Findings showed that the distribution of HRDs in the brain was similar to the distribution of Aβ deposits. Furthermore, the similarity between these distributions did not appear to be the result of random chance. The authors concluded that the presence of HRDs may constitute a precursor to amyloid plaque development and that a breakdown in microvasculature resulting from microhemorrhages relates to development of AD neuropathology. Similarly, findings of atherosclerosis in the circle of Willis among AD patients in Kalback et al. (2004) further implicate microvascular breakdown in AD. The authors suggested that the accumulation of amyloid plaques are actually a "defense mechanism" of the brain in response to changes in blood supply.

Castellani et al. (2006) provide some evidence to support theories suggesting that stress within the brain precedes the deposition of Aβ. These authors suggest that the lesions of AD are a consequence of brain pathology, such as oxidative stress, rather than the cause of pathology. They suggest that when neurons are confronted with oxidative

stress, they respond by increasing the production of Aβ, which correspondingly reduces oxidative stress. A review by De la Torre (2002) also provides evidence that hypoperfusion in the brain as the result of changes in blood supply due to hypertension or atherosclerosis leads to oxidative stress, which in turn leads to Aβ accumulation.

Another line of research has implicated insulin growth factor-I (IGF-I), a protein involved in neuronal growth and inhibition of apoptosis, in the pathogenesis of AD, particularly in the development of neurofibrillary tangles (NFTs; Watanabe et al., 2005). Furthermore, IGF-I appears to be involved in the clearance of Aβ from the brain (Watanabe et al., 2005). Low IGF-I concentrations are associated with cognitive decline (Dik et al., 2003). While these studies do appear to implicate decreased IGF-I in the development of AD lesions and cognitive impairment, the research into this relationship remains sparse. Future research is needed to further illuminate the mechanisms of IGF-I.

Lastly, some researchers have suggested that compromised function of the blood-brain-barrier (BBB) and the endothelial cells that constitute the BBB may contribute to AD. Zipser et al. (2007) suggested that Aβ is increased around microvessels in the brain in order to repair tears or shrinkage in the BBB due to inflammation or vascular injury. Kalback et al. (2004) further suggested that malfunction in the BBB results from hypoperfusion due to vascular compromise from hypertension or atherosclerotic lesions. Compromised BBB function can also be linked to the effects of insulin on amyloid accumulation. Insulin is transported through the BBB via insulin transporters (Craft & Wilson, 2004). However, if the BBB is compromised, this transportation process is disrupted, resulting in abnormal levels of insulin within the brain.

Regardless of the specific mechanism, all of these theories and biological links mentioned previously have a few aspects in common. Specifically, inflammation and oxidative stress have been mentioned frequently in regard to the development of AD. Inflammation due to insulin or disruption of inflammatory mechanisms of the immune system appears to contribute to amyloid deposition. This inflammation may result from microvascular injury resulting from reduced cerebral blood flow and hypoperfusion associated with hypertension, atherosclerosis, or infarction. Other consequences of inflammation and vascular injury include BBB compromise and altered metabolism, affecting especially the vulnerable hippocampus. Changes in metabolism may, in turn, affect levels of insulin and IDE within the brain, further increasing levels of Aβ within the brain. Unfortunately, no comprehensive theory relating vascular mechanisms to AD is available. It is important that researchers attempt to synthesize these findings to better understand how AD develops.

It should be noted that all of the cardiovascular risk factors reviewed offer the possibility of prevention of AD. Further illumination of vascular mechanisms of AD development and specific risk factors will provide opportunities not only for prevention but also for potential treatment. Therefore, the continued pursuit of the underlying pathogenesis of AD and its relation to cardiovascular factors is imperative.

APPENDIX B.

Expanded Methods

Data screening

Because the population of interest in the current study is older adults, individuals aged 44 and younger (n = 28) as well as those for whom age was unknown (n = 2) were excluded from the analyses. Furthermore, since education was used as a covariate for all subsequent analyses, subjects without data regarding level of education were excluded (n = 34). An additional 983 subjects for whom hypertension and diabetes diagnosis data were unavailable were excluded. Neuropsychological testing data for 1161 subjects was incomplete; thus, these subjects were not eligible for inclusion in the final analyses.

Data from the remaining 1041 subjects was screened for univariate and multivariate outliers. To investigate univariate outliers, z-scores for each diagnosis and disease subgroup (i.e. CN-HTN) were computed and boxplots were examined for each of the dependent variables. A subject's score was considered a univariate outlier if the z-score exceeded +/- 3.3 and was labeled as an extreme outlier on the boxplot graph when compared to the scores of other subjects within the same subgroup. Based on these criteria, 30 subjects had a score on one dependent measure that was considered a univariate outlier. These subjects included one from the CN-normal group, 15 from the CN-HTN group, 3 from CN-DM, 3 from CN-both, 3 from AD-neither, 14 from AD-HTN, 2 from AD-DM, and 3 from AD-both. As these subjects were believed to have come from the population of interest, they were not deleted from future analyses; instead, the outlying score were changed to the next highest/lowest score within the distribution in order to decrease their impact on the main analysis. Multivariate outliers were examined

by through Mahalanobis distance. The critical value for Mahalanobis distance was taken from the chi-square distrubtion [$x^2(14) = 36.12$] and any subjects with a distance exceeding this value were considered multivariate outliers. Based on this criterion, a total of 15 subjects were deleted from the analyses; thus, the final sample consisted of 1026 subjects.

Table 5. Demographic variables across diagnostic groups

	Age		Education		Gender		Race		Location	
	Mean	SD	Mean	SD	Male	Female	Cauc	AA	Roch	Jax
Full sample	78.32	7.71	12.76	3.00	350 (34.1%)	676 (34.1%)	905 (88.2%)	107 (10.4%)	906 (88.3%)	120 (11.7%)
Cognitively normal	77.70	7.80	13.02	2.94	225 (32.9%)	458 (67.1%)	582 (85.2%)	100 (14.6%)	570 (83.5%)	113 (16.5%)
AD	79.61	7.46	12.27	2.98	109 (36.5%)	190 (63.5%)	281 (94.0%)	5 (1.7%)	294 (98.3%)	5 (1.7%)
VaD	79.18	6.93	12.18	3.30	16 (36.4%)	28 (63.6%)	42 (95.5%)	2 (4.5%)	42 (95.5%)	2 (4.5%)

Note: AD = Alzheimer's Disease, VaD = Vascular dementia, SD = standard deviation, Cauc = Caucasian, AA = African American, Roch = Rochester, Jax = Jacksonville

Table 6. Means and standard deviations for assessment performance in the cognitively normal sample based on disease status

	All cognitively normal		Neither condition		HTN only		DM only		Both conditions	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
AVLT										
Immediate recall	6.68	2.92	6.81	2.88	6.75	2.93	6.49	3.28	6.27	2.78
Delayed recall	5.91	3.16	6.16	3.20	5.89	3.18	5.98	3.31	5.54	2.95
Recognition	12.20	2.51	12.36	2.65	12.11	2.53	12.37	2.10	12.18	2.31
WMS-R										
Logical Memory I	25.35	6.18	24.52	6.40	25.64	6.06	26.83	5.64	25.03	6.33
Logical Memory II	20.69	6.70	20.21	6.53	20.67	6.97	21.78	6.26	21.17	6.07
Visual Reproduction I	16.55	8.21	15.82	8.12	16.77	8.22	17.68	8.08	16.53	8.36
Visual Reproduction II	15.08	7.46	14.33	7.20	15.10	7.83	15.80	6.78	16.04	6.59
Boston Naming Test	50.11	7.68	48.79	8.42	50.63	7.22	49.44	9.27	50.77	7.05
COWAT	33.62	11.30	34.30	11.73	34.00	11.55	32.61	9.48	31.44	10.01
DRS										
Attention	34.64	2.00	34.61	2.08	34.63	2.00	35.07	1.85	34.52	1.96
Initiation-Perseveration	35.42	2.44	35.23	2.68	35.52	2.39	35.32	2.42	35.49	2.13
Construction	5.70	0.63	5.59	0.78	5.79	0.46	5.76	0.44	5.49	0.83
Conceptualization	35.85	3.03	35.41	3.55	36.05	2.80	36.71	2.29	35.50	3.07
Memory	23.01	1.84	23.02	1.69	22.97	1.88	23.34	2.29	23.01	1.76

Note: AVLT = Rey Auditory-Verbal Learning Test, WMS-R = Wechsler Memory Scales – Revised, COWAT = Controlled Oral Word Association Test, DRS = Mattis Dementia Rating Scale

Table 7. Means and standard deviations for assessment performance in the AD sample based on disease status

	All AD		*Neither condition*		*HTN only*		*DM only*		*Both conditions*	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
AVLT										
Immediate recall	1.32	1.56	1.73	1.95	1.17	1.39	1.68	1.54	1.10	1.65
Delayed recall	0.36	0.79	0.33	0.63	0.26	0.61	0.87	1.42	0.38	0.71
Recognition	6.95	3.97	6.90	3.83	6.82	3.85	7.50	4.34	7.03	4.40
WMS-R										
Logical Memory I	13.91	6.38	14.73	6.17	13.65	6.43	15.32	6.76	12.64	5.87
Logical Memory II	6.51	4.91	7.41	5.09	5.94	4.27	6.87	4.73	7.59	6.97
Visual Reproduction I	2.22	3.14	2.55	3.76	2.08	2.95	2.50	3.55	2.18	2.71
Visual Reproduction II	1.33	2.60	0.90	1.70	1.07	2.00	1.45	2.40	2.90	4.76
Boston Naming Test	35.18	12.56	35.00	13.04	34.49	12.28	38.68	13.76	35.10	11.84
COWAT	21.70	10.25	24.14	10.82	21.58	10.32	22.92	11.12	17.92	7.17
DRS										
Attention	32.89	3.11	33.47	2.59	32.98	2.76	32.87	3.81	31.79	4.14
Initiation-Perseveration	26.93	6.84	29.45	5.74	26.38	6.82	27.29	6.57	25.87	7.88
Construction	5.30	1.08	5.47	1.10	5.31	1.04	5.24	1.03	5.10	1.29
Conceptualization	30.66	5.38	30.55	5.13	30.88	5.44	31.08	5.60	29.41	5.24
Memory	14.04	3.82	13.67	2.88	13.82	3.65	14.47	4.00	15.10	5.12

Note: AVLT = Rey Auditory-Verbal Learning Test, WMS-R = Wechsler Memory Scales – Revised, COWAT = Controlled Oral Word Association Test, DRS = Mattis Dementia Rating Scale