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RELATIONS AMONG TYPE 2 DIABETES, ARTERIAL STIFFNESS AND COGNITIVE FUNCTIONING

by

Gregory A. Dore

B.A., University of Maine, 2004

A DISSERTATION

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

(in Psychology)

The Graduate School

The University of Maine

May, 2013

Advisory Committee:

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DISSERTATION ACCEPTANCE STATEMENT

On behalf of the Graduate Committee for Gregory A. Dore I affirm that this manuscript is the final and accepted dissertation. Signatures of all committee members are on file with the Graduate School at the University of Maine, 42 Stodder Hall, Orono, Maine.

Dr. Merrill F. Elias, Professor of Psychology Date

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RELATIONS AMONG TYPE 2 DIABETES, ARTERIAL STIFFNESS AND COGNITIVE FUNCTIONING

by Gregory A. Dore

Dissertation Co-Advisors: Dr. Merrill F. Elias, Dr. Michael A. Robbins

An Abstract of the Dissertation Presented
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Philosophy
(in Psychology)
May, 2013

Although the associations among diabetes mellitus, cognitive functioning and arterial stiffness have been explored previously, the degree to which arterial stiffness is responsible for the association between diabetes and cognitive function has not been examined. The primary aim of the current investigations is to examine the extent to which arterial stiffness mediates the association between diabetes and cognitive function, as well as the extent to which this indirect effect is modified by age and *APOE* genotype. The sample included 590 participants (age 23-94, 62% women, 12% African-American) from the seventh wave of the Maine-Syracuse Longitudinal Study. Individuals with history of stroke, probable dementia, and PWV error of estimate >0.20 were excluded. Diabetes was defined as elevated glucose or treatment. Pulse wave velocity was used to as an indirect measure of arterial stiffness. Multiple statistical methods were used to examine the association between diabetes and cognitive function, as well as between PWV and cognitive function. Then, path analysis was used to examine the direct and indirect (through PWV) associations between diabetes and cognitive function. With adjustment for demographic and CVD risk variables,

associations between diabetes and multiple measures of cognitive ability were observed for the *APOE-ε4* carriers only. PWV was related to multiple cognitive measures, and this association was modified by age such that the lowest performance was observed in older individuals with elevated PWV. When diabetes, PWV and cognitive function were included together in the analysis of paths between variables, an indirect association between diabetes and cognitive function through PWV was observed, such that diabetes related to higher PWV, and lower cognitive function in older APOE-ε4 carriers. These findings may have important clinical implications with regard to attenuating the pronounced association between diabetes and cognitive function observed for persons who carry the *APOE*-ε4 allele. Accelerated arterial stiffness may possibly be treated by the same methods that are used to treat hypertension. Clinical trials are necessary to determine if modification of levels of PWV by drugs and other treatments will lead to an improvement in cognitive performance. Treatment specific to *APOE* genotype are also a possibility.

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LIST OF ABBREVIATIONS

A1C	hemoglobin A1C
AIx	augmentation index
AGE	advanced glycation end-product
APOE	apolipoprotein E
aPP	aortic pulse pressure
BMI	body mass index
BP	blood pressure
CAA	cerebral amyloid angiopathy
CES-D	Center for Epidemiologic Studies – Depression scale
COWA	Controlled Oral Word Associations
CRP	C-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
HDL	high density lipoprotein
LDL	low density lipoprotein
MAP	mean arterial pressure
MSLS	Maine Syracuse Longitudinal Study
PWV	pulse wave velocity
SBP	systolic blood pressure
VSOM	Visual-Spatial Organization and Memory

1. INTRODUCTION

Many studies, including studies with the Maine Syracuse Longitudinal Study (MSLS) have shown that cardiovascular risk factors have an inverse relationship with level of cognitive function (M. F. Elias et al., 2004; M. F. Elias, Robbins, P. K. Elias, & Streeten, 1998; M. F. Elias, Robbins, et al., 2009). That is, higher risk for cardiovascular events is associated with lower levels of cognitive performance, accelerated decline in cognitive performance, and increased risk of developing dementia (M. F. Elias, P. K. Elias, Robbins, Wolf, & D'Agostino, 2001; Elias, Goodell, & Dore, 2012). One such risk factor for cardiovascular events, diabetes mellitus (diabetes), has been shown to relate to cognitive function, cognitive decline, and dementia (Roriz-Filho et al., 2009).

Diabetes is not only related to cognitive function, but also to other cardiovascular risk factors. For example, individuals with diabetes have higher blood pressure (BP), higher levels of adiposity, and higher levels of inflammatory biomarkers (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004). The associations between diabetes and cognitive function remain after statistical adjustment for these risk factors (M. F. Elias, P. K. Elias, Sullivan, Wolf, & D'Agostino, 2005; Dore, M. F. Elias, Robbins, P. K. Elias, & Nagy, 2009), suggesting that diabetes affects cognitive function independently of these variables. However, the diabetic state may worsen the impact of other risk factors on cognitive function (Robbins, M. F. Elias, Budge, Brennan, & P. K. Elias, 2005).

Another risk factor for cardiovascular mortality and morbidity, arterial stiffness, is also related to cognitive function (M. F. Elias, Robbins, Budge, Abhayaratna, Dore, & P. K. Elias, 2009), cognitive decline (Benetos, Watfa, Hanon, et al., 2012; Watson, Sutton,

Rosano, et al., 2011) and diabetes (see Stehouwer, Henry, & Ferreira, 2008 for review). Arteries stiffen with aging (Noon, Trischuk, Gaucher, Galante, & Scott, 2008), and this stiffening is accelerated in diabetic individuals (Benetos et al., 2002).

Although the associations between diabetes and cognitive function, diabetes and arterial stiffness, and arterial stiffness and cognitive functioning have been explored in previous studies, the degree to which arterial stiffness mediates the association between diabetes and cognitive function is unclear. Therefore, the primary aim of the current investigations is to examine the extent to which arterial stiffness mediates the association between diabetes and cognitive function.

In Section 1.1, we review and describe the various types of diabetes (Section 1.1.1), descriptive data related to the prevalence of type 2 diabetes (Section 1.1.2), and measures used to define type 2 diabetes in the context of an epidemiological study (Section 1.1.3) and discuss measures of type 2 diabetes available in the MSLS (Section 1.1.4). In Section 1.2, we explore the concept of arterial stiffness (Section 1.2.1) and describe the measures used to assess arterial stiffness (Section 1.2.2).

Section 1.3 describes the associations among diabetes, arterial stiffness, and cognitive function. First, the literature relating diabetes to lowered cognitive function is reviewed (Section 1.3.1), followed by a review of the literature relating increased arterial stiffness to lowered cognitive function (Section 1.3.2). Finally, a theoretical mediational model is presented. In this model, the association between diabetes and lowered cognitive function is accounted for, at least in part, by pulse wave velocity, the gold standard index of arterial stiffness (Section 1.3.3).

Section 1.4 outlines hypotheses and objectives of the current study. Section 2 outlines the sample used (Section 2.1), procedures used for data collection (Section 2.2), cognitive variables used in the MSLS (Section 2.3), and concludes with a discussion of the data analysis methods used in the current study (Section 2.4).

1.1. Type 2 Diabetes – Definition and Related Measures

1.1.1. Subtypes of Diabetes

There are four distinct classes of diabetes mellitus: type 1 diabetes, type 2 diabetes, gestational diabetes, and other types of diabetes caused by specific genetic defects, pancreatic disease, or drugs/chemicals (American Diabetes Association, 2012a). Type 1 diabetes was traditionally termed "insulin-dependent diabetes mellitus" or "juvenile-onset diabetes", because of it usually occurs early in life, due to an autoimmune reaction resulting in β-cell destruction and a corresponding lack of insulin production. Treatment with insulin is thus required for survival. In contrast, type 2 diabetes, in the past called "non-insulin-dependent diabetes mellitus" or "adult-onset diabetes" because it usually occurs later in life, is characterized not by lack of insulin production, but insulin resistance (decreased sensitivity of body tissues to insulin) and hyperglycemia (elevated levels of glucose in the blood). The pathophysiology of gestational diabetes is similar to that of type 2 diabetes (glucose intolerance), but this form of diabetes improves or disappears following delivery. Type 2 diabetes accounts for 90-95% of all diabetes cases, and risk factors for this class of diabetes include both modifiable (e.g. obesity, hypertension, physical inactivity) and non-modifiable (e.g. age, race/ethnicity, and family

history) factors (Deshpande, Harris-Hayes, & Schootman, 2008). For these reasons this investigation focuses on type 2 diabetes.

1.1.2. Prevalence and Incidence of Type 2 Diabetes

In epidemiology, prevalence is defined as the number of cases at a specific point in time and incidence as the number of new cases. From 1980 to 2007, the prevalence of self-report of diagnosed diabetes in the U.S. increased from 2.5% to 5.9%. From 1980 to 1995, the prevalence of diabetes remained relatively stable at about 3%, then began to increase from 3.3% (8.6 million) in 1996 to 5.9% (17.4 million) in 2007. This increase does not seem to be completely due to the increasing age of the U.S. population in general (Centers for Disease Control, 2010) even though the prevalence of diabetes increases dramatically with advancing age (Centers for Disease Control and Prevention, 2008). As previously noted, approximately 90-95% of these cases are type 2 diabetes. With respect to incidence, in 2007, 1.6 million individuals aged 20 years or older were newly diagnosed with diabetes (Centers for Disease Control and Prevention, 2008).

1.1.3. Objective Measures Utilized in the Diagnosis of Type 2 Diabetes

Diabetes is typically diagnosed on the basis of plasma glucose levels. Specifically, subjects with fasting glucose levels greater than or equal to 126 mg/dl (7.0 mmol/l) are considered to be diabetic (American Diabetes Association, 2012a). This glycemic cut-point was established because retinopathy (microvascular pathology in the retina) was found to be relatively absent in individuals with glucose levels below these

cut-points. Above these levels, prevalent retinopathy increases in a linear fashion (American Diabetes Association, 2012a). Previous research has shown that retinopathy is reflective of cerebrovascular abnormalities (Cooper et al., 2006). Although there are issues with self-report data, some studies of cognition have employed self-report of diabetes or history of diabetes from medical records (Gregg et al., 2000; Grodstein, Chen, Wilson, & Manson, 2001). The justification for these methods has been the fact that many patients accurately report their medical history of diagnosis. However, it is estimated that 26% of diabetes cases go undiagnosed (Centers for Disease Control and Prevention, 2008). Therefore objective measures are preferable and will be used to define diabetes in the current study.

Recently, a more long-term measure of glucose levels, glycated hemoglobin (hemoglobin A1C), has been used to assess glucose levels, and therefore risk of retinopathy associated with diabetes (American Diabetes Association, 2012b). This index is not directly applicable to the proposed work as the MSLS does not have data for hemoglobin A1C. However, well established measures widely used in clinical practice are used in the current study.

1.1.4. Measures of Diabetes Available in the MSLS

The MSLS is a 35-year longitudinal study of hypertension and related cardiovascular risk factors as they relate to cognitive functioning (Elias, Goodell, Robbins, in press; Elias, Robbins, et al., 2004). It consists of seven serial examinations (waves), with each examination separated by a mean difference of 4.5 years. However, until wave 6, the information obtained about diabetes comprised predominantly self-

report measures of diagnosis, type, and medications from waves 1 to 5. Beginning with wave 6 and continuing though wave 7, fasting blood samples were drawn at each wave of the study and a number of assays were performed, including plasma glucose levels. Therefore, for the current study, which involves wave 7 data, objective data (blood glucose level determinations) are used to ascertain diabetic versus non-diabetic status.

In the following section the concept of arterial stiffness (measured by pulse wave velocity) is introduced and methods of measurement are discussed. The importance of these definitions and this phenomenon in relation to the proposed work are then explained.

1.2. Arterial Stiffness – Mechanisms and Measurement Methods.

1.2.1. Arterial Stiffness – Mechanisms

During the course of "normal" aging, the human arterial system undergoes a process of arterial stiffening, that is, a decrease in distensibility of the large arteries (i.e. the aorta, carotid, iliac, femoral, and brachial arteries). This process is driven by several factors, including the reduction of arterial elastin content, an increase in collagen content, and thickening of the arterial wall. When the left ventricle contracts during systole, a pressure wave (or "pulse wave") is created, and this pressure wave propagates along the aorta to distal arterial bifurcations. The wave is then reflected back toward the heart. In healthy younger individuals, this reflected wave is timed so that it augments diastolic blood pressure. With the increased stiffness in older age, the pulse wave travels through the vasculature faster, and therefore is reflected back sooner, resulting in an augmentation

of systolic blood pressure. This phenomenon manifests itself as an increase in pulse pressure (the difference between systolic and diastolic blood pressure) and a corresponding higher prevalence of isolated systolic hypertension in older individuals (Greenwald, 2007). Figure 1.1 illustrates the differences in pulse waves between younger and older individuals.

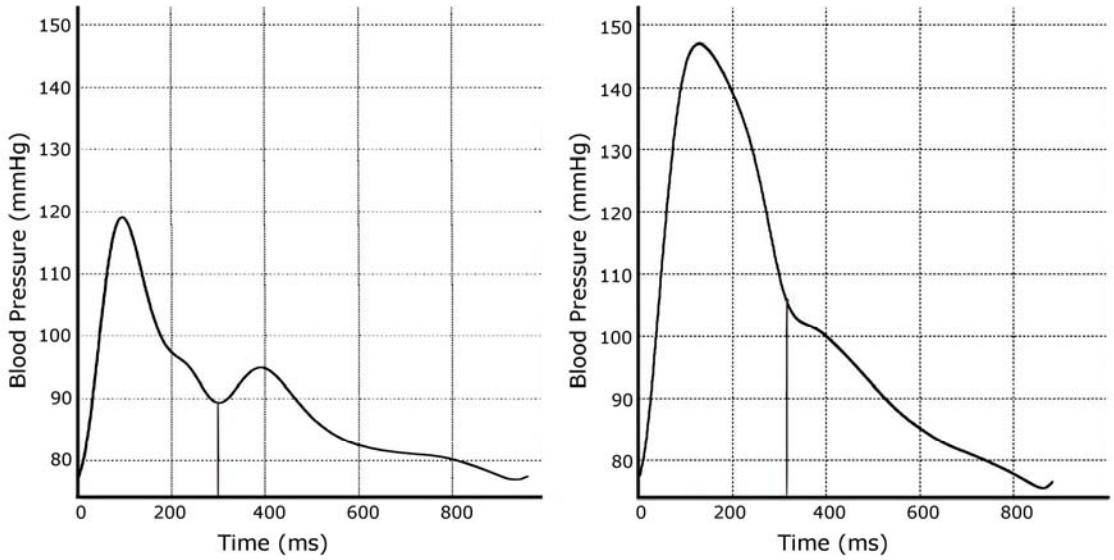

Figure 1.1. Pulse pressure waveforms in younger (left) and older (right) individuals.

In addition to its relationship with aging, several pathological processes are related to increased arterial stiffness. These include endothelial dysfunction, atherosclerosis, and smooth muscle cell function. Age-related arterial stiffness is accelerated by disorders such as diabetes and hypertension and is predictive of cardiovascular morbidity and mortality (Wang, Keith, Struthers, Feuerstein, 2008).

1.2.2. Measures of Arterial Stiffness

Due to the increase in pulse pressure observed with increased arterial stiffness, pulse pressure has been used as a measure of arterial stiffness in previous studies (P.K. Elias, M. F.. Elias, Robbins, & Budge, 2004). However, as pulse pressure is derived from peripheral (i.e. brachial) blood pressure measures, it may not reflect stiffness of the central arteries (Laurent, Cockcroft, Van Bortel, et al., 2006). Aortic pulse wave velocity (PWV), the speed of the pressure wave along the aorta, is considered the gold standard non-invasive measure of central arterial stiffness (Laurent et al., 2006), and is reliably assessed by applanation tonometry (see Section 2.2). Additionally, the percentage increase of the systolic pressure attributable to the reflected wave can be determined (see Figure 1.1) through analysis of the pulse wave; this measure is referred to as the augmentation index (AIx). Both of these measures have been used to measure arterial stiffness in previous studies (see review by O'Rourke & Hashimoto, 2008), and are available at wave 7 of the MSLS.

Due to the limitations of the augmentation index (Cheng, Tang, Cheng, Huang, Wang, 2007), this measure will only be used in secondary analyses in the current study. As PWV is the preferred measure of arterial stiffness (Laurent et al., 2006), this measure will be the primary predictor. The main limitation of PWV has been absence of normative data by age, but these data are now available from two major studies, (Reference Values for Arterial Stiffness Collaboration, 2010; M. F. Elias, Dore, et al., 2011), including the Maine Syracuse Longitudinal Study.

In the following section, previous research relating diabetes and arterial stiffness to cognitive function will be reviewed. Additionally, the rationale for considering PWV as a possible mediator between diabetes and cognitive function will be discussed.

1.3. Components of the Path from Diabetes to Cognitive Function

1.3.1. Diabetes and Cognitive Function

The relationship between diabetes and cognitive function has been investigated extensively and a number of recent reviews are available (Biessels, Deary, & Ryan, 2008; Kodl & Seaquist, 2008; Roriz-Filho, Sa-Roriz, Rosset, et al., 2009; van den Berg, Reijmer, & Biessels, 2009; Wrighten, Piroli, Grillo, & Reagan, 2009). Although some studies suggest that cognitive function is unrelated to diabetic status (e.g. Asimakopoulou, Hampson, & Morrish, 2002), a majority of studies indicate that diabetes is associated with lowered cognitive function (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009). In the following section, the literature relating diabetes to cognitive function, including relevant MSLS investigations, will be reviewed. Although diabetes has also been related to dementia (Cukierman, Gerstein, & Williamson, 2005), the proportion of persons with dementia in the MSLS study is very low (0.3%). Consequently, the current study and the remainder of the discussion on diabetes and cognitive function focus on cognitive performance in non-demented individuals.

In the following section, we describe cognitive abilities and domains associated with diabetes. Here, the term "ability" refers to measures of performance indexed by a single test. In contrast, the term "domain" is used to refer to performance indexed by multiple tests (i.e. composite scores derived from factor analysis).

1.3.1.1. Cognitive Abilities and Domains Associated with Diabetes. An association between diabetes and cognitive function was first described in 1922 (Miles & Root, 1922). Diabetic individuals performed more poorly than non-diabetic comparison groups on tests of memory, arithmetic, and psychomotor speed. Since then, there have been at least 278 studies on the topic and a wider variety of cognitive abilities have been measured. Although the specific cognitive tests used vary across studies, some generalizations can be made concerning the cognitive abilities related to diabetes. The most common finding is that diabetic subjects perform more poorly than nondiabetic subjects on tests of attention, verbal and non-verbal memory, and processing speed (Kodl & Seaquist, 2008; Roriz-Filho et al, 2009; van den Berg, Reijmer, & Biessels, 2009). There is less agreement on other cognitive abilities, but some investigators have reported that executive function (Kodl & Seaquist, 2008; Roriz-Filho et al, 2009), psychomotor speed, and complex motor function (Kodl & Seaquist, 2008) are lowered in diabetic individuals compared to non-diabetic individuals. A pattern of cognitive domains consistent with the literature have been found in the MSLS.

1.3.1.2. Findings from the MSLS. In the MSLS, cognitive function is indexed by several composite scores derived by principal components and factor analyses (M. F. Elias et al. 2006) and thus with the exception of one cognitive outcome variable (WAIS Similarities), assesses cognitive domains. These include Working Memory, Verbal Memory, Visual-Spatial Memory/Organization, and Scanning and Tracking. The test battery also includes the Similarities subtest of the Wechsler Adult Intelligence Scale. A Global composite was constructed from each of the tests making up the composites and the Similarities Test. Similarities is always used as a separate measure as it loaded at an

approximately equal level on each of the other composite scores (factors) during the factor analytic process. These composites have been used in multiple studies and are now incorporated into the literature and thus a new factor analysis was not done in this investigation (Elias, M. F., Robbins, et al., 2004). The tests and the composite scores are summarized in Section 2.3.

Figure 1.2 shows results in a recent study (Dore, Elias, Robbins, Elias, 2009) of diabetes and cognitive performance. Diabetic study participants exhibited lower performance (compared with non-diabetic participants) on Similarities, and all of the Composite score measures, with the exception of the Verbal Memory composite (see Figure 1.2), although the trend was for diabetic subjects to also perform more poorly on this composite. These data, along with many previous findings discussed in the previous section provide strong evidence that diabetes is associated with multiple domains of cognitive function.

1.3.1.3. APOE Genotype as an Effect Modifier. Cardiovascular disease risk factors other than diabetes have also been shown to relate to cognitive function. Of these risk factors, presence of at least one apolipoprotein E (*APOE*) ε4 allele, is of particular interest for the current study, as this factor has been shown to modify the association between diabetes and cognitive function.

The presence of at least one apolipoprotein E (*APOE*) ε4 allele is associated with dementia and lowered levels of cognition (Farrer, Cupples, Haines, et al., 1997; Small, Rosnick, Fratiglioni, et al., 2004). Aside from serving as a CVD risk factor in its own right, presence of the *APOE* ε4 allele has been shown to modify the effects of other CVD risk factors (e.g., M. F. Elias et al., 2006), including diabetes, on cognitive function

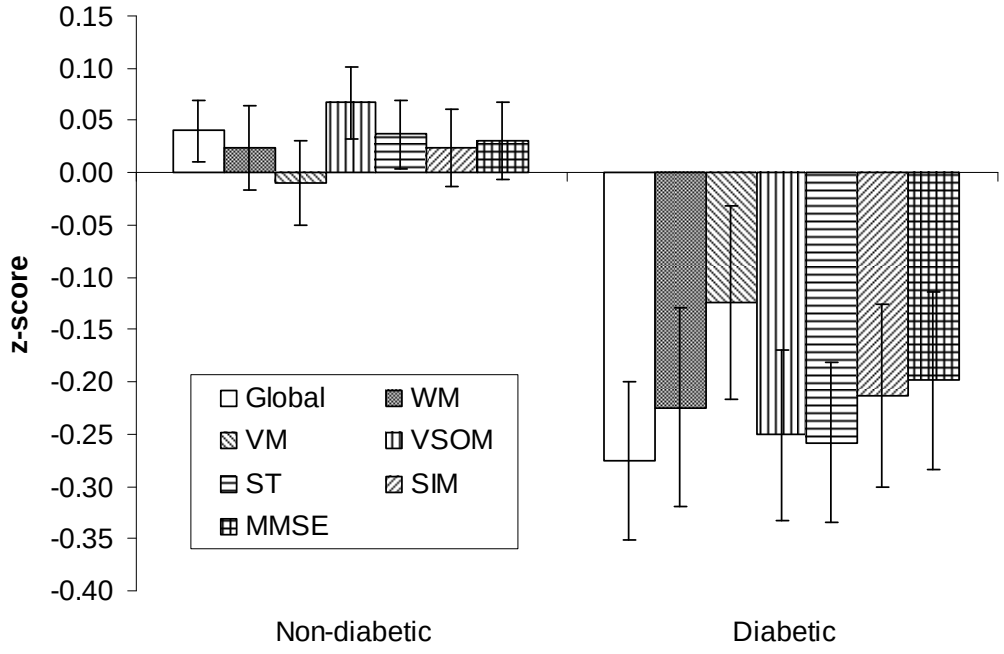

Figure 1.2. Adjusted means and standard errors illustrating the relationship between diabetes and cognitive outcome variables in the MSLS. Means are adjusted for diabetes, APOE group, age, education, sex, race/ethnicity, SBP, smoking, triacylglycerols, chronic kidney disease, BMI, alcohol consumption, depressed mood, CRP, prevalent CVD, and tHcy. All p-values for comparisons between non-diabetic and diabetic subjects are $p < .05$, with the exception of Verbal Memory ($p = .25$). Adapted from Dore, M. F. Elias, Robbins, & P. K. Elias (2009).

VM = Verbal Memory
WM = Working Memory
VSOM = Visual-Spatial Memory/Organization
ST = Scanning & Tracking
SIM = Similarities
MMSE = Mini-Mental State Examination

(Haan, Shemanski, Jagust, et al., 1999; Dore, Elias, Robbins, Elias, & Nagy, 2009). A recent study using data from the MSLS found that diabetic *APOE* ε4 carriers exhibited lower levels of cognitive performance, although non-diabetic *APOE* ε4 carriers and non-carriers did not differ in terms of performance on cognitive measures. That is, lowered cognitive performance was observed in diabetic subjects, and this effect was more pronounced in those with at least one *APOE* ε4 allele.

1.3.2. Arterial Stiffness and Cognitive Functioning

As is true for other risk factors for CVD, higher levels of arterial stiffness have been shown to relate to lowered levels of cognitive function (M. F. Elias, Robbins, et al., 2009), and more accelerated cognitive decline (Laurent, Cockroft, van Bortel,et al., 2006; Waldstein, Rice, Thayer, Najjar, Scuteri, & Zonderman, 2008; Benetos, Watfa, Hanon, et al., 2012; Watson, Sutton, Rosano, et al., 2011) in older, but not younger individuals. A recent study using data from wave 7 of the MSLS (M. F. Elias, Robbins, et al., 2009) found that arterial stiffness, as indexed by PWV, interacted with age in relation to multiple cognitive domains. The combination of older age and higher PWV was found to be associated with the lowest level of cognitive performance. Similarly, in the Baltimore Longitudinal Study of Aging, Waldstein, Rice, Thayer, Najjar, Scuteri, & Zonderman (2008) found an interaction between PWV and cognitive change, such that individuals with the highest PWV exhibited the most pronounced rates of cognitive decline. Therefore, all statistical analyses involving arterial stiffness (described in later sections) involved examination of interactions with age.

1.3.3. Arterial Stiffness as a Mediator between Diabetes and Cognitive Performance

Diabetes is associated with increased cardiovascular disease, including peripheral arterial disease, coronary heart disease, and cerebrovascular disease (Kannel & McGee, 1979). The vascular nature of the chronic complications of diabetes is not surprising, given that the prevalence of retinal microvascular lesions forms the basis for defining diabetes based on circulating glucose levels (American Diabetes Association, 2012a).

The association between diabetes and increased arterial stiffness is well-established (see Stehouwer et al., 2008 for review). Increased atherosclerotic plaque deposition, exacerbated by the increased inflammatory (i.e. immune) response characteristic of the diabetic state is one mechanism which leads to increased arterial stiffness. Chronic hyperglycemia results in the accelerated formation of advanced glycation endproducts (AGEs), promoting the formation of oxidized low density lipoproteins (LDL; Basta, Schmidt, & De Caterina, 2004), which is more atherogenic than normal LDL (Xu, He, & King, 2005). In addition, increased oxidative stress (increased production of reactive oxygen species), possibly due to increased AGE formation (Stitt, Jenkins, & Cooper, 2002) or resulting directly from chronic hyperglycemia (Brownlee, 2001), may decrease bioavailability of nitric oxide (a vasodilator) and activate the protein kinase C pathway, resulting in maintenance of a chronic inflammatory state (Jenkins, Hill, & Rowley, 2008). In addition to factors leading to increased atherosclerotic plaque deposition, diabetes is also associated with increased arterial calcification, further increasing arterial stiffness (Chen & Moe, 2003).

Increased systemic inflammation (Teunissen et al., 2003), arterial calcification (Rosano, Naydeck, Kuller, Longstreth, & Newman, 2005), oxidative stress (Berr,

Richard, Roussel, & Bonithon-Kopp, 1998), and increased atheroma deposition (Romero et al., 2009) have all been associated with decreased levels of cognitive performance, brain infarction, and higher severity of white matter lesions. The extent to which arterial stiffness (perpetuated by the above mechanisms) mediates the association between diabetes and cognitive function is unclear; the primary objective of the proposed study is to address this question. In the next section, we discuss these objectives in relation to specific hypotheses.

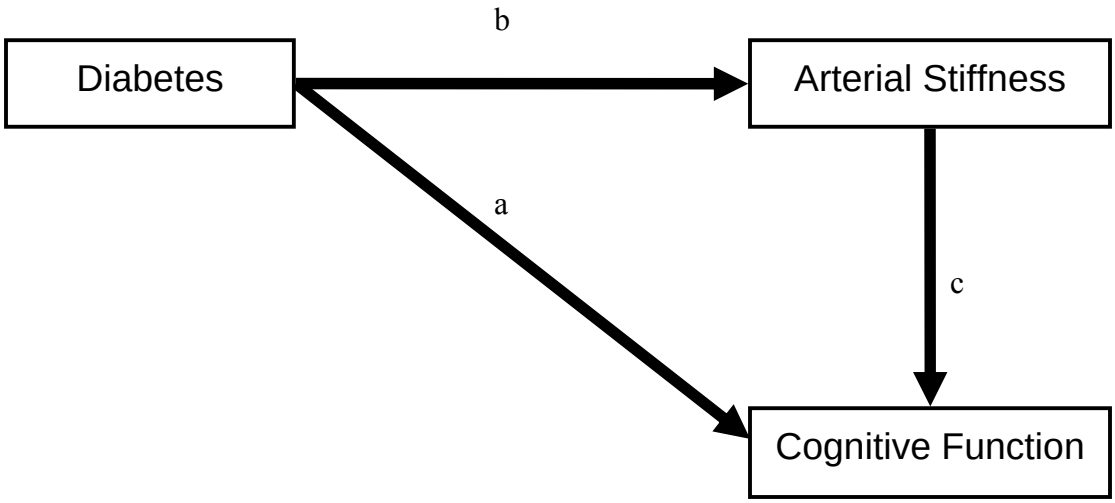

Figure 1.3. Simplified mediational model.

1.4. Study Hypotheses in Relation to Objectives.

To our knowledge, there are no studies that have investigated the extent to which arterial stiffness mediates the association between diabetes and cognitive function. As can be seen in Figure 1.3, this mediational model consists of two important paths: 1) the direct association between diabetes and cognitive function (represented by path a); and 2) the indirect association between diabetes and cognitive function through PWV (represented by paths b and c). Given that cognitive function is the outcome of interest,

before analyzing a full path model, the association between diabetes and cognitive function, and the association between PWV and cognitive function will be examined. The following section describes the above objectives and related hypotheses in more detail.

Objectives of the proposed work together with associated hypotheses were as follows:

1. To examine the association between diabetes and cognitive function at wave 7 of the MSLS, as modified by *APOE* genotype.

   Hypothesis: Previous associations observed at wave 6 of the MSLS (Dore et al., 2009) will be replicated at wave 7.

   Rationale. This step is necessary to establish this association for the later path analysis aspect of the study (see hypothesis 3). Additionally, this step will be used to establish covariates to be used in later path analyses. It is also important because previous work with the MSLS data have used Wave 6 data.

2. To determine whether previously reported associations between arterial stiffness and cognitive function in cross-sectional studies will be observed at wave 7 of the MSLS.

   Hypothesis: Consistent with a previous MSLS study, arterial stiffness (as measured by pulse wave velocity) will interact with age such that the lowest cognitive

performance levels will be observed for older individuals. Most importantly, using new methods for assessing moderated mediation (discussed in Section 2.4), we will determine the ages at which this negative association between pulse wave velocity and cognitive function is observed.

3. To determine, using path analysis, whether arterial stiffness mediates the association between diabetes and cognitive functioning using cross-sectional data at wave 7. Additionally, to examine whether age, a strong predictor of PWV, moderates the effect of arterial stiffness as an intervening variable between diabetes and cognitive function.

   Hypothesis. Arterial stiffness (defined as PWV in primary analyses) will mediate the association between diabetes and cognition as indicated by path analysis; specifically, there will be an indirect effect observed for diabetes through PWV on cognitive function. Additionally, this relationship will be modified by age and *APOE* genotype, such that the association between arterial stiffness and cognitive function (and therefore the indirect path from diabetes through PWV to cognitive function) will be of higher magnitude for older individuals with an *APOE*-ε4 allele.

2. METHODS

2.1. Sample and Design

Cross-sectional data were taken from the seventh serial repetition (wave 7) of the Maine-Syracuse Longitudinal Study, a community-based study of CVD risk factors and cognition begun in Syracuse, New York in 1974. Recruitment and data collection procedures have been described in detail previously (Elias et al., 2006). The MSLS is an open-enrollment longitudinal study in which new individuals are recruited at each wave. Wave 7 was the first and only wave in which PWV was measured.

Of the 626 participants (24 to 93 years of age) with PWV at wave 7, participants were excluded in the following sequence: 1) history of acute stroke (n= 14); 2) probable dementia (n= 2); 3) PWV error of estimate >0.20 (n= 20); and missing APOE genotype data (n= 44). The PWV error of estimate is a measure of the quality of the PWV measurements, with lower values being a sign of higher-quality PWV assessments. Measurements with PWV error of estimate >0.20 are not considered suitable for analysis.

The final sample consisted of 546 participants. We did not exclude persons with diagnosed mild cognitive impairment because we wished to retain the full range of variation in continuously distributed test scores, while eliminating persons who showed major decrements in performance level and who were often able to complete only few, if any, of the tests in our battery (i.e. those with dementia). Acute stroke can have devastating effects on cognition and serves as a major confounder and thus is excluded in many studies of CVD risk factors in relation to cognitive performance (M. F. Elias et al., 2012; M. F. Elias et al., in press).

History of acute stroke, defined as occurrence of a focal neurological deficit of acute onset persisting more than 24 hours, was based on self-report and record review indicating a diagnosis of acute stroke. The clinical diagnosis of dementia, as in the case in the Framingham Heart Study (M. F. Elias et al., 2000) was based on MSLS expert committee review (neuropsychologists, social psychologists, geriatric physician) of cognitive data including the MMSE and confirmatory medical records including significant other informant report. The National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria were used for this diagnosis (McKhann, Drachman, Folstein, et al., 1984).

2.2. Procedures

Participants completed the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) within 1 week prior to reporting to the MSLS laboratory (Syracuse, New York) for neuropsychological testing. Following a fast from midnight, a blood sample was drawn in the morning and was followed by a light breakfast and interview (including medical history). Subsequently, after supine rest for 15-minutes, five reclining, five standing, and five sitting automated blood pressure (BP) measurements (GE DINAMAP 100DPC-120XEN; GE Healthcare) were obtained sequentially with a 5-minute interval between each set of measurements.

Neuropsychological testing followed the BP measurements. Tests were presented in the same order for each individual because of the necessity of uniform sequencing and standard presentation of the Wechsler Adult Intelligence Scale subtests, the Wechsler

Memory Scale subtests, trails A and B and other measures. Brief rest periods were given whenever participants appeared to be in need of a rest before continuing. All assay methods used to derive data on independent variables and covariates have been described previously (Elias et al, 2006).

Diabetes was defined by treatment with insulin, oral glucose-lowering agents, or by fasting glucose level of 126 mg/dl (7 mmol/l) or higher. Objective data on duration of diabetes were not available to the study, but persons with diabetes at wave 7 (objectively defined) were asked to estimate the duration of their diabetes and this was used as a descriptive variable, as is the case in most previous work.

Pulse wave velocity was assessed noninvasively in a supine position, using the SphygmoCor system (AtCor Medical) with applanation tonometry (M. F. Elias, Robbins, et al., 2009; M. F. Elias, Dore, et al., 2011). Carotid-femoral path length was measured as the difference between the surface distances joining the suprasternal notch, the umbilicus, and the femoral pulse, as well as the suprasternal notch and the carotid pulse. Carotid-femoral transit time was estimated in 8 to 10 sequential ECG-gated femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. The foot of the pulse wave was identified using the intersecting tangent method. PWV was calculated as the carotid-femoral path length divided by the carotid-femoral transit time (O'Rourke, Pauca, & Jiang, 2001). This is a noninvasive and reproducible method to determine arterial stiffness (Laurent, Cockcroft, Van Bortel, et al., 2006).

Age and education are measured in years. Ethnicity includes African American, Hispanic, Asian American, Caucasian, and American Indian. Because of the small

number of minority participants (~15%), and the small number of non-African-American minorities in particular (~3%), this variable is coded as African American vs. other.

Standard *APOE* genotyping used polymerase chain reaction and restriction enzyme digest with HhaI (Hixson & Vernier, 1990). Serum creatinine was determined using a two-point rate test type on a Johnson and Johnson VITROS instrument (Ortho Clinical Diagnostics). Coefficients of variation for these procedures were less than 5.0%. Estimated glomerular filtration rate was derived from the four-variable (serum creatinine, age, sex and ethnicity) Modification of Diet in Renal Disease study equation (Levey AS, Bosch JP, Lewis JB et al., 1990; Rule, Gusak, Pond, et al., 2004). Chronic renal disease (yes/no) was defined as estimated glomerular filtration rate <60 ml min–1 (1.73 m2)–1. Determinations of high sensitivity C-reactive protein (CRP), plasma homocysteine (tHcy), triglycerides and glucose were performed as previously described (Elias et al., 2006). Mean systolic BP (SBP) and diastolic BP (DBP) were determined by taking the average of 15 BP measurements (described previously). Additional covariates used in various analyses included: BMI (kg/m2), self-report of number of cigarettes smoked per week, alcohol consumption (g/week), and self-reported presence of CVD confirmed by medical records and/or treatment. As in the Framingham Heart Study (Elias et al., 2004), CVD was defined as the presence of any one of the following: (1) myocardial infarction (3.7%); (2) coronary artery disease (7.5%); (3) heart failure (1.4%); (4) angina pectoris (3.6%); (5) transient ischemic attack (1.9%).

2.3. Cognitive Tests and Domains

We employed the Similarities subtest from the Wechsler Adult Intelligence Scale, and four composite test scores derived from a previous factor analysis of individual tests in the MSLS battery for this study population (Elias et al., 2006). The four composite scores were Visual–Spatial Memory and Organization (Visual Reproductions—Immediate and Delayed, Matrix Reasoning, Block Design, Object Assembly, and the Hooper Visual Organization Test), Scanning and Tracking (Trail-Making A and B, Digit Symbol Substitution, and Symbol Search), Verbal Memory (Logical Memory—Immediate and Delayed, and the Hopkins Verbal Learning Test) and Working Memory (Digit Span Forward and Backward, Letter–Number Sequencing, and Controlled Oral Word Associations). The Similarities subtest was used as a separate measure because it loaded in an approximately equal manner on multiple composite scores in the previous factor analysis. In addition to the factor analyses, reducing the number of outcome variables, we followed a protection rule in which none of the results for individual tests would be interpreted in the absence of a significant result for the Global composite score.

More detailed descriptions of the individual tests are given in Table 2.1. Consistent with previous MSLS studies, scores (time in seconds) for Trails A and B were log transformed. Then, to construct the composite scores, the individual tests related to each composite were expressed in z scores and added (Elias et al., 2006). The composite scores were again transformed to z scores. Composite scores were used to decrease error

Table 2.1. Descriptions of the cognitive tests contributing to each composite score indexing a cognitive domain[a].

Test Composite/ Tests Included in the Composite	Cognitive Ability Measured
Verbal Episodic Memory	
Logical Memory-Immediate Recall [b]	Immediate memory, verbal
Logical Memory-Delayed Recall [b]	Delayed memory, verbal
Hopkins Verbal Learning Test	Verbal learning and memory
Visual-Spatial Organization/Memory	
Visual Reproductions-Immediate Recall [b]	Immediate recall, visual memory, and visual-spatial problem solving
Visual Reproductions-Delayed Recall [b]	Delayed recall, visual memory and visual-spatial problem solving
Matrix Reasoning [c]	Abstract reasoning and pattern recognition
Block Design [d]	Visual-spatial perception, organization and construction
Object Assembly [d]	Speed of visual-spatial organization
Hooper Visual Organization	Visual-spatial organization; some demands on executive function
Scanning and Tracking	
Trail Making A [e]	Visual scanning and tracking; concentration and attention
Trail Making B [e]	Trails A plus demands on executive function abilities
Digit Symbol Substitution [d]	Psychomotor performance
Symbol Search [c]	Visual processing speed
Working Memory	

Table 2.1. (cont.)

Test Composite/ Tests Included in the Composite	Cognitive Ability Measured
Working Memory	
Digit Span Forward [d]	Attention and concentration
Digit Span Backward [d]	Attention, concentration, and working memory
Letter-Number Sequence [c]	Information processing while holding information in memory
Controlled Oral Word Associations	Verbal fluency and executive functioning
Executive Function	
Trail Making B [e]	Trails A plus demands on executive function abilities
Controlled Oral Word Associations	Verbal fluency and executive functioning
Similarities[d]	Verbal intelligence and abstract reasoning

[a]The tests employed in each composite score/domain define the abilities measured by that domain.

[b]Origin Wechsler Memory Scale-Revised

[c]Origin Wechsler Adult Intelligence Scale III

[d]Origin Wechsler Adult Intelligence Scale

[e]Origin Halstead-Reitan Neuropsychological Test Battery

associated with analyses involving multiple related cognitive outcomes and to permit us to examine theoretically relevant cognitive domains. These composite scores were derived from principal components analyses and factor analyses; this procedure is outlined in a previous study (M. F. Elias, et al., 2006).

This linear transformation results in a mean of zero and an SD of 1.00 for each test and enables expression of regression coefficients for the cognitive measures in terms of SD units. The previously identified composites (factors) (Elias et al., 2006) were confirmed via replication of the factor analysis for the present sample. In addition to composite scores, a Global composite score was calculated by averaging the z scores for all individual tests (excluding the MMSE). The MMSE was considered to be a separate measure of mental status.

The University of Maine Institutional Review Board approved the protocol for this investigation. Informed consent for data collection was obtained from all participants.

2.4. Statistical Methods

The major statistical analyses consisted of 3 phases: 1) covariate selection from candidate covariates for use in extended models; 2) analysis of the bivariate relationships forming the component paths using basic and extended covariate models; and 3) analysis of the complete path model.

2.4.1. Covariate Selection

Previous empirical data, theory and statistical methods were used in conjunction to select covariates. Beginning with a list of candidate covariates theoretically and

empirically relevant to the associations among diabetes, arterial stiffness, and cognitive function, final models were obtained by following 2 steps: 1) potential covariates which did not show a relationship with diabetes, the primary predictor of interest, were dropped; and 2) a stepwise backward elimination was performed, with a basic set of covariates fixed in the model, and any covariates not meeting the inclusion criteria ($p < .10$) were excluded from the models. These steps were followed with the goal of obtaining the most parsimonious covariate set and to limit loss of statistical power and sensitivity in path analysis which is associated with the use of an excessive number of covariates.

The basic covariate set, age, education, gender, race/ethnicity, height, weight, heart rate, and mean arterial pressure (MAP) was used in all analyses. Additional candidate covariates included additional variables which were found to differ between diabetic and non-diabetic individuals. A candidate variable may be defined as one that is considered for a covariate set based on a bivariate relationship with diabetes but subject to elimination given the need to avoid multicollinearity. Where more than one method of assessing a covariate was available, alternate measures of these covariates were included in *sensitivity analyses*, i.e. secondary and tertiary analysis done to test robustness of the statistical effect with different definitions of parameters or different models. Candidate covariates included components of the metabolic syndrome (elevated blood pressure, dyslipidemia, and adiposity), renal function, smoking, alcohol consumption, depressed mood, cardiovascular disease, plasma homocysteine, heart rate, and antihypertensive drug treatment.

2.4.2. Regression Analyses

Following preliminary analyses and covariate selection, multiple linear regression analyses (SAS PROC GLM) were employed to examine the cross-sectional associations between 1) diabetes (independent variable) and cognitive function (dependent variable) and 2) pulse wave velocity (independent variable) and cognitive function (dependent variable). These analyses involved first using a basic covariate set (age, education, gender, race/ethnicity, height, weight, heart rate, MAP) and then forming an extended covariate set, adding variables surviving the covariate selection procedures outlined above. All covariates within a covariate set were entered simultaneously with the independent variable.

As previous research from the MSLS has shown that the relationship between diabetes and cognitive function is modified by *APOE* genotype, diabetes × *APOE* genotype interactions were assessed. Similarly, previous MSLS studies have shown that age modifies the association between PWV and cognitive function, PWV × age interactions were also examined. As the PWV × age interaction involves two continuous variables, the nature of this interaction was probed using both classic methods (i.e. splitting the distribution of age into tertiles), as well as a new method outline by Hayes (2012). This method involves examining the path model outlined in Figure 2.1 and computing predicted slopes for PWV at each value of age, using the Johnson-Neyman technique. This method has the advantage of keeping both components of the interaction term as continuous variables, rather than grouping them using arbitrary cutpoints.

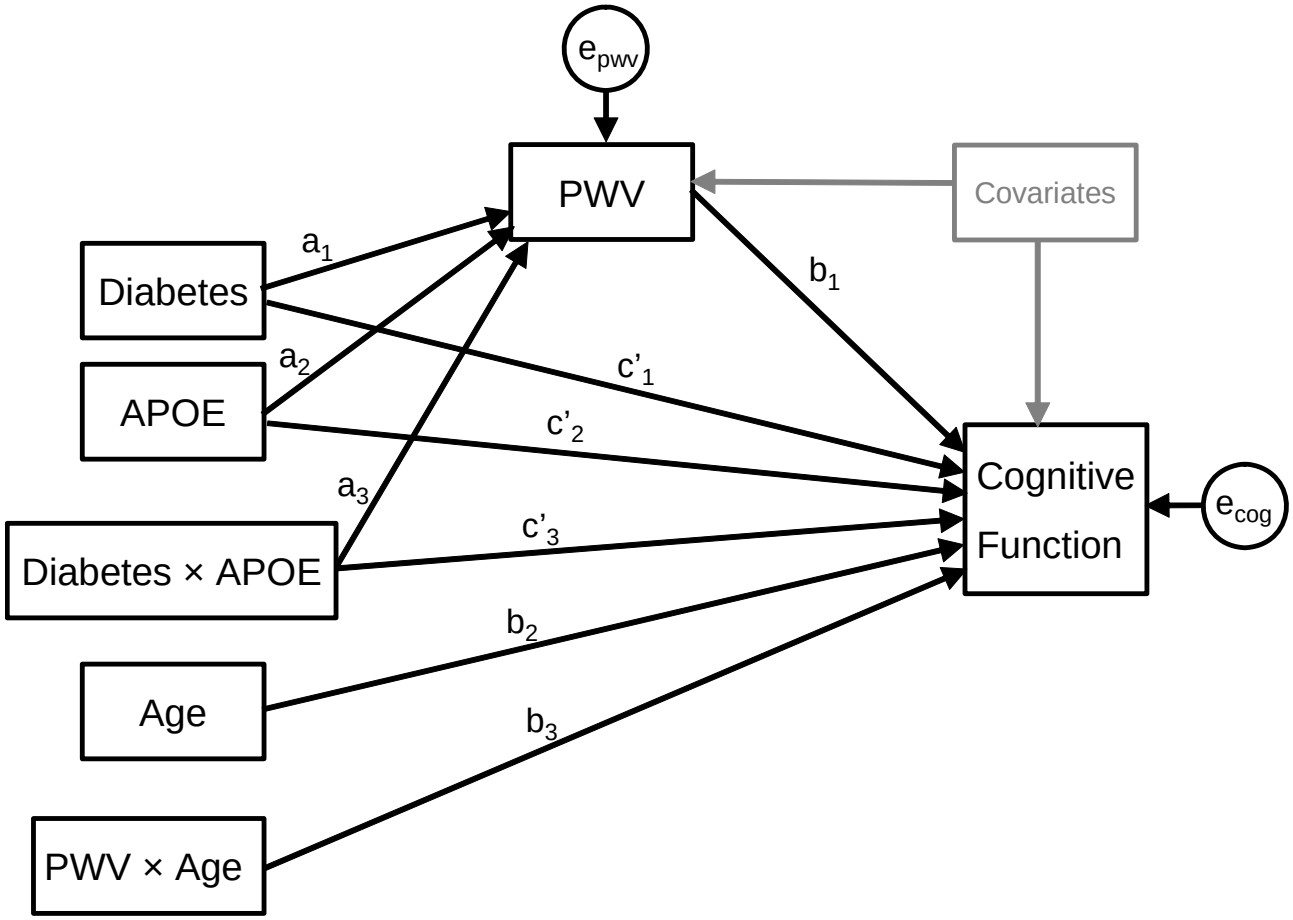

Figure 2.1. Path model used to assess the conditional (moderated by age and APOE) indirect effect of diabetes on cognitive function through PWV. Hayes (2012) model 22

Conditional indirect effect of *diabetes* on *cognition* through *PWV* = $(a_1 + a_3[APOE])\ (b_1 + b_3[age])$
Conditional direct effect of *diabetes* on *cognition* = $c'_1 + c'_3[APOE]$

Further, this method also allows determination of the values of age for which there is a significant relationship between PWV and cognitive function, without the loss of power associated with other methods.

2.4.3. Path Analyses

Following the assessment of diabetes × *APOE* and PWV × age interactions in relation to cognitive function, these interactions were combined into the more comprehensive path model shown in Figure 2.1. It should be noted that in discussing this model, the term "effect" is used not with the implication of a causative relationship between predictors and outcomes, but rather to use terminology consistent with path analysis. In this model, there are two effects of interest: 1) the direct effect of diabetes in relation to cognitive function and 2) the indirect effect of diabetes through PWV on cognitive function. This model also includes both the diabetes × *APOE* interaction and the PWV × age interaction. As can be seen in the footnote to Figure 2.1, the direct effect of diabetes on cognitive function is conditional on *APOE* genotype. Similarly, the indirect effect of diabetes on cognitive function is conditional on both *APOE* and age. Specifically, the conditional direct effect of diabetes on cognitive function is the combination of the diabetes → cognitive function path (c'_1) and the diabetes × *APOE* → cognitive function path (c'_3). Similarly, the conditional indirect effect is a combination of the diabetes → PWV path (a_1), the diabetes × *APOE* → PWV path (a_3), the PWV → cognitive function path (b_1), and the PWV × age → cognitive function path (b_3).

Using this model, conditional direct effects for diabetes were computed for each *APOE* group, and conditional indirect effects for diabetes were computed for each *APOE*

group. As conditional indirect effects involved continuous age, two methods were used to probe these effects: 1) examination of the indirect effects at the 5^{th}, 25^{th}, 50^{th}, 75^{th}, and 95^{th} percentiles of age, and 2) examination of indirect effects across the complete observed range of age. All standard errors and confidence intervals were computed using bootstrapping (5000 samples), as recommended by the author of the macro (Hayes, 2012).

3. RESULTS

3.1. Demographic and health variables

Table 3.1 shows demographic and health variables for non-diabetic and diabetic individuals separately. Non-diabetic and diabetic individuals differed on all variables with the exception of age, smoking habits, DBP, mild renal dysfunction, depressed mood, and *APOE* genotype. Diabetic individuals tended to have higher SBP, higher BMI and waist circumference, higher triglycerides, lower HDL cholesterol, and were more likely to be hypertensive. Interestingly, diabetic individuals showed lower total and LDL cholesterol levels, most likely due to the higher proportion of diabetic participants treated for elevated cholesterol, possibly due to an emphasis on diabetes control.

3.2. Covariate Selection

Table 3.1 shows all possible variables for consideration for backward elimination, i.e. possible confounders. Of these, the following differed between non-diabetic and diabetic individuals: alcohol consumption, triglycerides, plasma homocysteine, serum creatinine, CES-D score, history of CVD, treatment with antihypertensive medications, and treatment with lipid-lowering medications. We did not adjust for antidiabetic medications, because 91% of the diabetic individuals were treated for diabetes at Wave 7 of the MSLS. Further, because the majority (89%) of

Table 3.1. Demographic information and health characteristics

Variable	Non-diabetic (n = 462)	Diabetic (n = 84)	p
Age (years), M (SD)	63.9 (12.7)	65.3 (9.9)	0.287[1]
Education (years), M (SD)	14.9 (2.7)	13.6 (2.9)	<0.001
Alcohol (oz/wk), M (SD)[2]	1.4 (2.4)	0.8 (2.0)	0.015[1]
Cigarettes per week, M (SD)[2]	6.7 (33.5)	9.0 (37.6)	0.562
Total cholesterol (mg/L), M (SD)	191.9 (37.9)	165.5 (38.9)	<0.001
LDL-cholesterol (mg/L), M (SD)	115.4 (32.1)	92.4 (28.6)	<0.001
HDL-cholesterol (mg/L), M (SD)	54.9 (15.7)	44.9 (12.0)	<0.001[1]
Triglycerides (mg/L), M (SD)[2]	108.9 (63.4)	146.9 (130.1)	0.010[1]
Glucose (mg/L), M (SD)	92.3 (10.8)	131.5 (38.2)	<0.001[1]
Plasma homocysteine (μmol/L), M (SD)[2]	9.9 (3.2)	11.2 (3.9)	0.007[1]
Serum creatinine (μmol/L), M (SD)[2]	1.0 (0.2)	1.2 (0.6)	0.008[1]
Systolic blood pressure (mmHg), M (SD)	128.3 (20.0)	135.3 (19.8)	0.003
Diastolic blood pressure (mmHg), M (SD)	76.8 (9.7)	78.3 (11.2)	0.210
Mean arterial pressure (mmHg), M (SD)	94.0 (11.9)	97.3 (12.8)	0.020
Body mass index (kg/m^2), M (SD)	29.1 (6.0)	32.6 (7.9)	<0.001[1]
Waist circumference (cm), M (SD)	92.4 (15.1)	103.6 (14.6)	<0.001
CES-D score, M (SD)[2]	7.5 (7.2)	9.7 (8.9)	0.037[1]
Duration of diabetes (years), M (SD)	-	10.6 (9.0)	-
Women, n (%)	302 (65.4)	37 (44.1)	<0.001
African-American, n (%)	46 (10.0)	17 (20.2)	0.014
Depressed mood, n (%)	52 (11.4)	15 (17.9)	0.105
Drinker, n (%)	239 (51.7)	25 (29.8)	<0.001
Smoker, n (%)	37 (8.0)	7 (8.3)	0.831
History of CVD, n (%)[2]	51 (11.0)	18 (21.4)	0.012
Mild renal dysfunction, n (%)	126 (27.3)	27 (32.1)	0.358
Hypertensive, n (%)	265 (57.4)	73 (86.9)	<0.001
Antihypertensive medications, n (%)	230 (49.8)	72 (85.7)	<0.001
Cholesterol medications, n (%)	149 (32.3)	55 (65.5)	<0.001
APOE-ε4 allele, n (%)	137 (29.7)	26 (31.0)	0.797

Note: t-tests were used for continuous variables; Fisher's exact test was used for categorical variables

[1]unequal variances; Satterthwaite approximation used.
[2]candidate variables for backward elimination procedure

M = mean; SD = standard deviation

hypertensive individuals were treated for hypertension at Wave 7 we could not use treatment for hypertension as a covariate. Moreover, many investigators argue that it is the observed blood pressure level, not the medicated blood pressure level, that is critical in the destructive effects of blood pressure on cognitive function (Elias et al., 2004). Controlled clinical trials have been mixed with regard to the improvement in cognitive function with treatment for hypertension. Where treatment has affected cognitive function, effects have been modest, if not trivial (Elias, Goodell, & Dore, 2012).

The remaining variables listed above were defined as candidate variables and added to a model including the major predictors and covariates in the current study (diabetes, PWV, age, education, gender, ethnicity, height, weight, heart rate, and MAP). Stated differently, the basic model above was fixed in the regression model, and then a backward elimination ($\alpha = 0.10$) was performed using the candidate variables as defined above.

Table 3.2 shows variables surviving the backward elimination (remaining significant at $p < .10$) for each of the cognitive outcome variables. CES-D, alcohol consumption, triglycerides, and CVD were each related to at least one cognitive outcome. Therefore, these variables were added to the basic model to form the extended model. Thus, the following two models were used for the following analyses: (1) the basic model (age + education + gender + ethnicity + height + weight + heart rate + MAP), and (2) the extended model (basic + CES-D + alcohol consumption + triglycerides + CVD).

Table 3.2. Variables surviving backward elimination (p = 0.10) for each of the cognitive outcome variables.

Cognitive Outcome	Predictor	b	SE	p
Global	CES-D	-0.017	0.004	<0.001
Verbal Memory	Alcohol consumption	0.030	0.016	0.070
VSOM	CES-D	-0.017	0.005	<0.001
Scanning & Tracking	CES-D	-0.021	0.004	<0.001
Working Memory	Triglycerides	-0.0010	0.0005	0.046
Similarities	CES-D	-0.014	0.005	0.009
Executive Function	CES-D	-0.011	0.005	0.027
	CVD	0.207	0.113	0.068

Full backward elimination model[1]:diabetes, PWV, age, education, gender, ethnicity, height, weight, heart rate, MAP, alcohol consumption, triglycerides, CES-D, CVD, tHcy

[1]The following variables were fixed in the backward elimination model: diabetes, PWV, age, education, gender, ethnicity, height, weight, heart rate, and MAP were fixed in the model.

Table 3.3. Regression coefficients (b) and standard errors (SE) for the diabetes × *APOE* interaction.

	Basic Model		Extended Model	
Cognitive Outcome	b	SE	b	SE
Global	-0.489**	0.180	-0.437*	0.178
Verbal Memory	-0.482*	0.216	-0.470*	0.217
VSOM	-0.213	0.194	-0.174	0.194
Scanning & Tracking	-0.474**	0.182	-0.403*	0.178
Working Memory	-0.498*	0.225	-0.447*	0.226
Similarities	-0.600**	0.216	-0.562**	0.217
Executive Function	-0.353	0.211	-0.278	0.210

**p< 0.01; *p< 0.05

Basic model = age, education, sex, ethnicity, heart rate, height, weight, MAP
Extended model = age, education, sex, ethnicity, heart rate, height, weight, MAP, alcohol consumption, triglycerides, CES-D, CVD

3.3. Diabetes × APOE Genotype Interaction

Table 3.3 shows regression coefficients for the diabetes × *APOE* genotype interaction in relation to cognitive outcome measures. This interaction was significant for all cognitive outcomes, with the exception of the Visual-Spatial Organization and

Memory (VSOM) and Executive Function composites. This pattern of results was the same with adjustment for the basic and extended models.

The nature of the diabetes × *APOE* interaction, with adjustment for the basic model, is shown in Figure 3.1. Diabetic *APOE*-ε4 carriers performed lower than all other groups on the Global ($p< 0.01$), Working Memory ($p< 0.01$), Verbal Memory ($p< 0.05$), Scanning and Tracking ($p< 0.01$) composites and Similarities ($p< 0.05$). No other group differences were observed for any cognitive outcome variables (all $p> 0.23$). The pattern of results was the same with adjustment for the extended model.

Additionally, we examined the association between the diabetes × *APOE* genotype interaction and the individual tests within the VSOM and EF composites. This was done in order to determine if the diabetes × *APOE* interaction was associated with any of the individual tests. For VSOM, the interaction effect was not related to any of the individual tests (p range = 0.08-0.76). For EF, the interaction term was related to Trails B ($p= 0.005$), but not COWA ($p= 0.44$).

3.4. PWV × Age Interaction

As can be seen in Table 3.4, the PWV × age interaction was significant for all cognitive outcome measures, with the exception of the Working Memory composite. This was true for the basic and extended models.

Table 3.5 illustrates the nature of the PWV × age interaction with results of separate regression analyses by age tertile (<59 years, 59 – 69 years, and >69 years). This approach represents the more classic method of probing interactions with continuous variables, i.e. the association between PWV and cognitive function was examined within age groups. For younger individuals, a generally positive association between PWV and

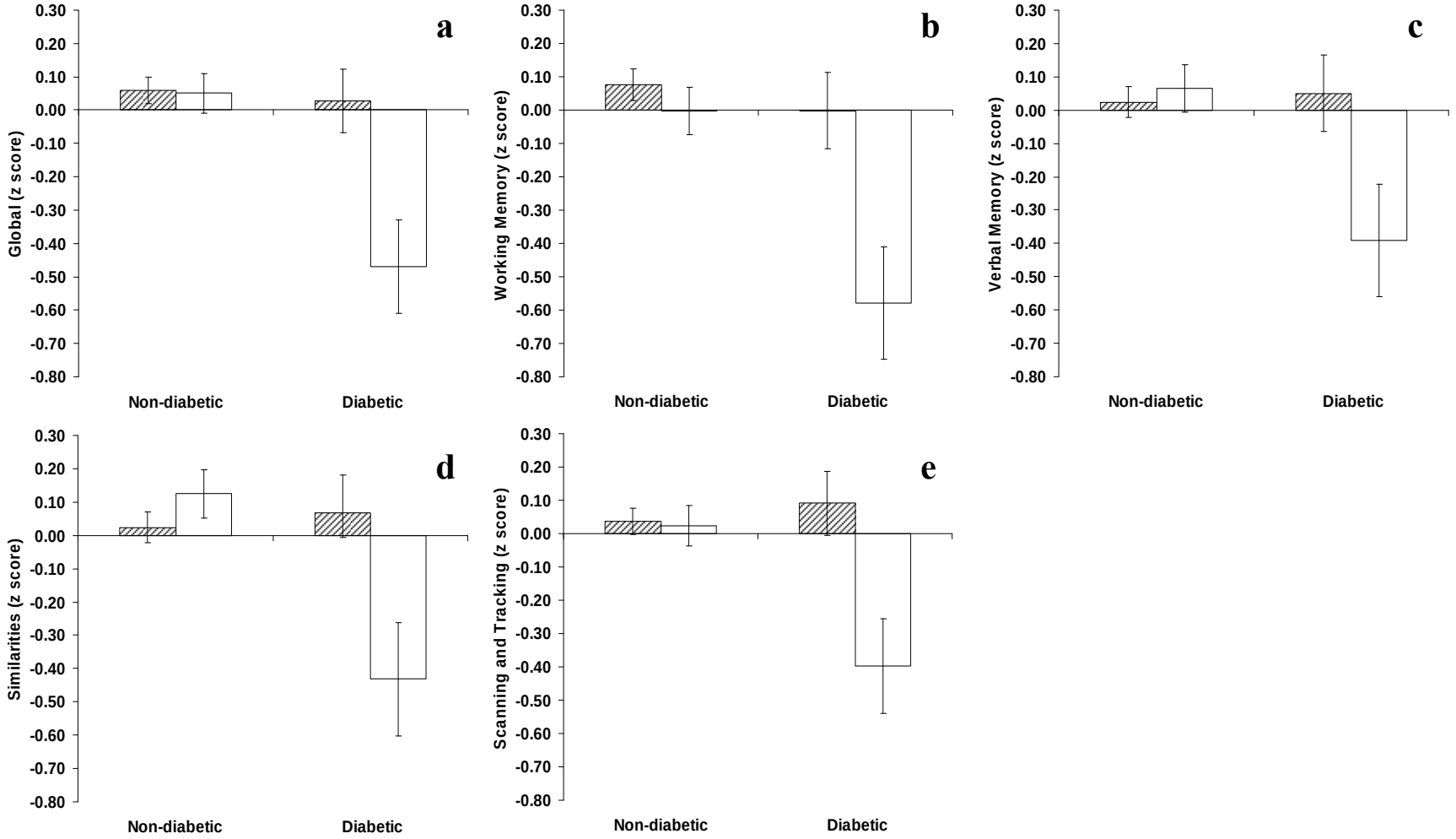

Figure 3.1. Adjusted (least squares) means for cognitive outcome measures by diabetic status and APOE group for: **(a)** the Global composite; **(b)** the Working Memory composite; **(c)** the Verbal Memory composite; **(d)** the Similarities subtest; and **(e)** the Scanning and Tracking composite. Means are adjusted for age, education, gender, ethnicity, height, weight, heart rate, and MAP (basic model). **Cross-hatched bars, no *APOE*-ε4; white bars, *APOE*-ε4. Error bars represent standard error of the mean**

Table 3.4. Regression coefficients (b) and standard errors (SE) for the PWV × age interaction.

	Basic Model		Extended Model	
Cognitive Outcome	b	SE	b	SE
Global	-0.0037***	0.0010	-0.0035***	0.0010
Verbal Memory	-0.0037**	0.0012	-0.0036**	0.0012
VSOM	-0.0039***	0.0010	-0.0036***	0.0010
Scanning & Tracking	-0.0027**	0.0010	-0.0023*	0.0010
Working Memory	-0.0018	0.0012	-0.0018	0.0012
Similarities	-0.0028*	0.0012	-0.0026*	0.0012
Executive Function	-0.0038**	0.0011	-0.0035**	0.0011

Basic model = age, education, sex, ethnicity, heart rate, height, weight, MAP

Extended model = age, education, sex, ethnicity, heart rate, height, weight, MAP, alcohol consumption, triglycerides, CES-D, CVD

cognitive outcome measures was observed. For the middle age tertile, PWV slopes were close to zero. A negative association between PWV and cognitive outcomes was observed for the oldest age tertile. Figures 3.2 – 3.4 show the relationship between PWV and the Global composite for the <59, 59-69, and >69 age groups, respectively.

Figure 3.5 shows the nature of the interaction using the Johnson-Neyman technique for the basic model. It will be recalled that this method, which estimates PWV slopes and 95% confidence intervals for the Global composite for all ages within the range of the data generated, provides PWV slopes for the full age range. It may be seen that PWV was significantly and positively related to the Global composite for individuals under 51 years of age, and was significantly and negatively related to the Global composite for individuals above 71 years of age. These associations are also illustrated in Figure 3.6, which shows predicted Global Composite z-scores by age and PWV. The pattern of results was similar for other cognitive outcomes, and with adjustment for the

Table 3.5. Regression coefficients (b) and standard errors (SE) expressing the association between PWV and cognitive function by age tertiles (separate regression analyses done for each age group).

		Age Group		
Cognitive Outcome		age< 59[1]	Age 59 – 69[2]	Age > 69[3]
Global	b	0.046	-0.003	-0.043*
	SE	0.038	0.027	0.019
Verbal Memory	b	0.089*	-0.005	-0.045*
	SE	0.043	0.033	0.023
VSOM	b	0.071†	0.011	-0.045*
	SE	0.040	0.028	0.022
Scanning & Tracking	b	-0.010	-0.011	-0.031
	SE	0.039	0.027	0.020
Working Memory	b	-0.014	-0.016	-0.023
	SE	0.052	0.037	0.021
Similarities	b	0.073	0.007	-0.013
	SE	0.048	0.031	0.024
Executive Function	b	0.007	-0.013	-0.032
	SE	0.048	0.032	0.021

†p< 0.10; *p< 0.05; **p< 0.01; ***p<0.001

[1]n = 175
[2]n = 176
[3]n = 195

model: PWV, age, education, sex, ethnicity, heart rate, height, weight, MAP

NOTE: Similar [but non-significant] results are obtained for the younger individuals when age<50 is used (n = 69)

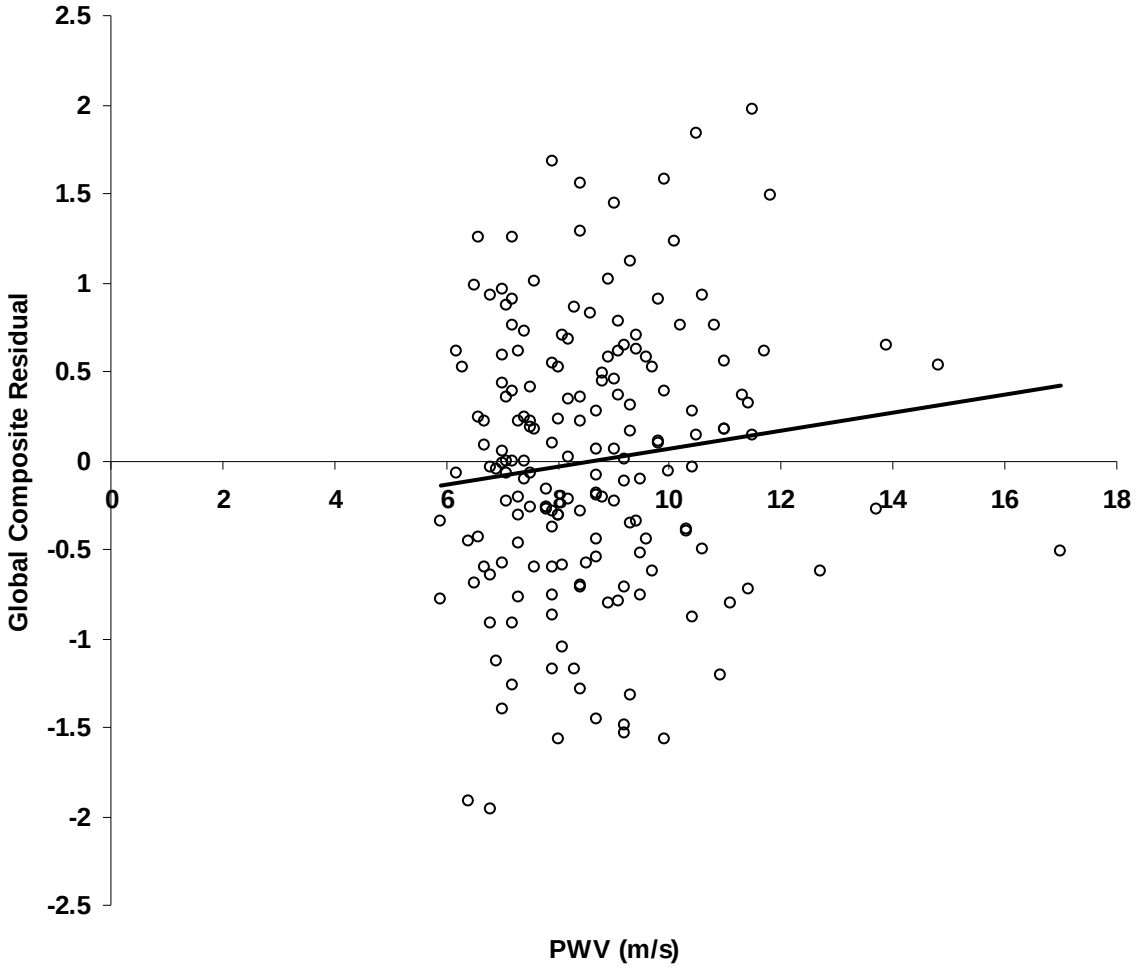

Figure 3.2. Relationship between PWV and Global Composite residuals for individuals under 59 years of age. Adjusted for age, education, sex, ethnicity, heart rate, height, weight, MAP

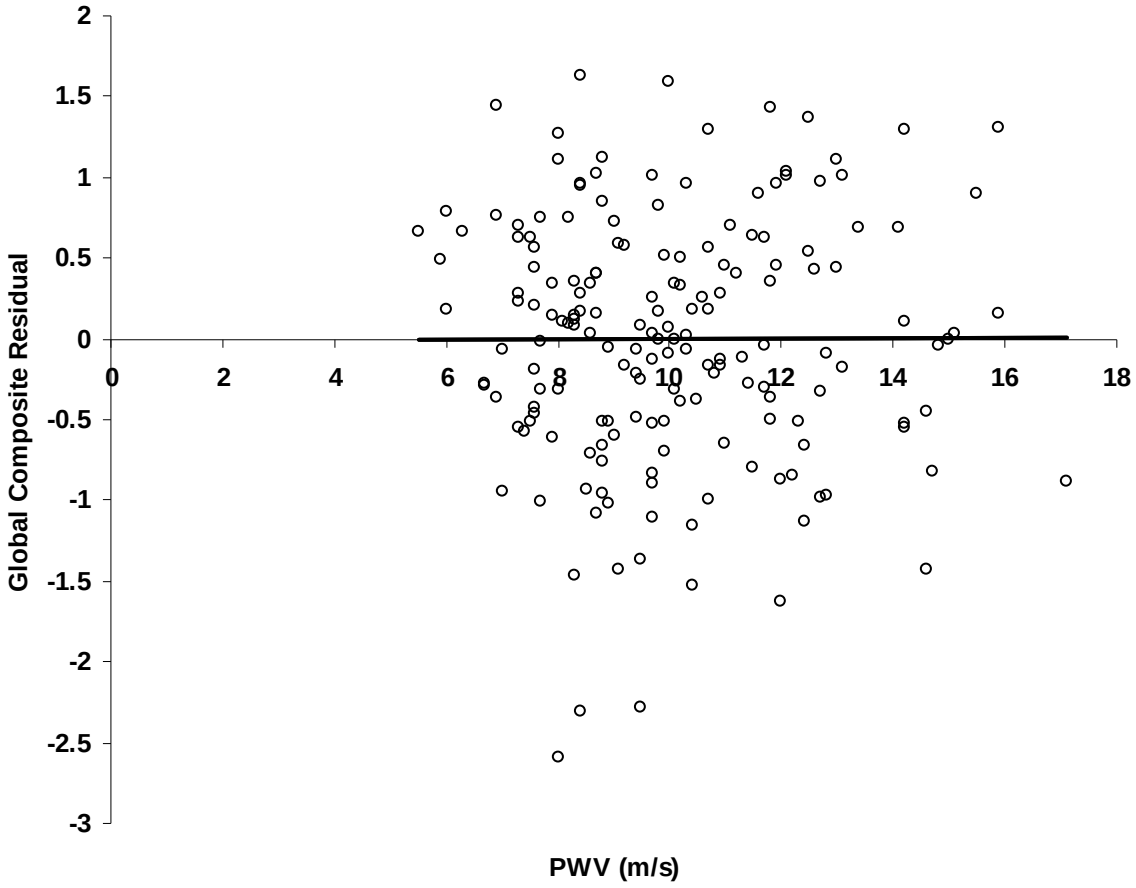

Figure 3.3. Relationship between PWV and Global Composite residuals for individuals 59 – 69 years of age. Adjusted for age, education, sex, ethnicity, heart rate, height, weight, MAP

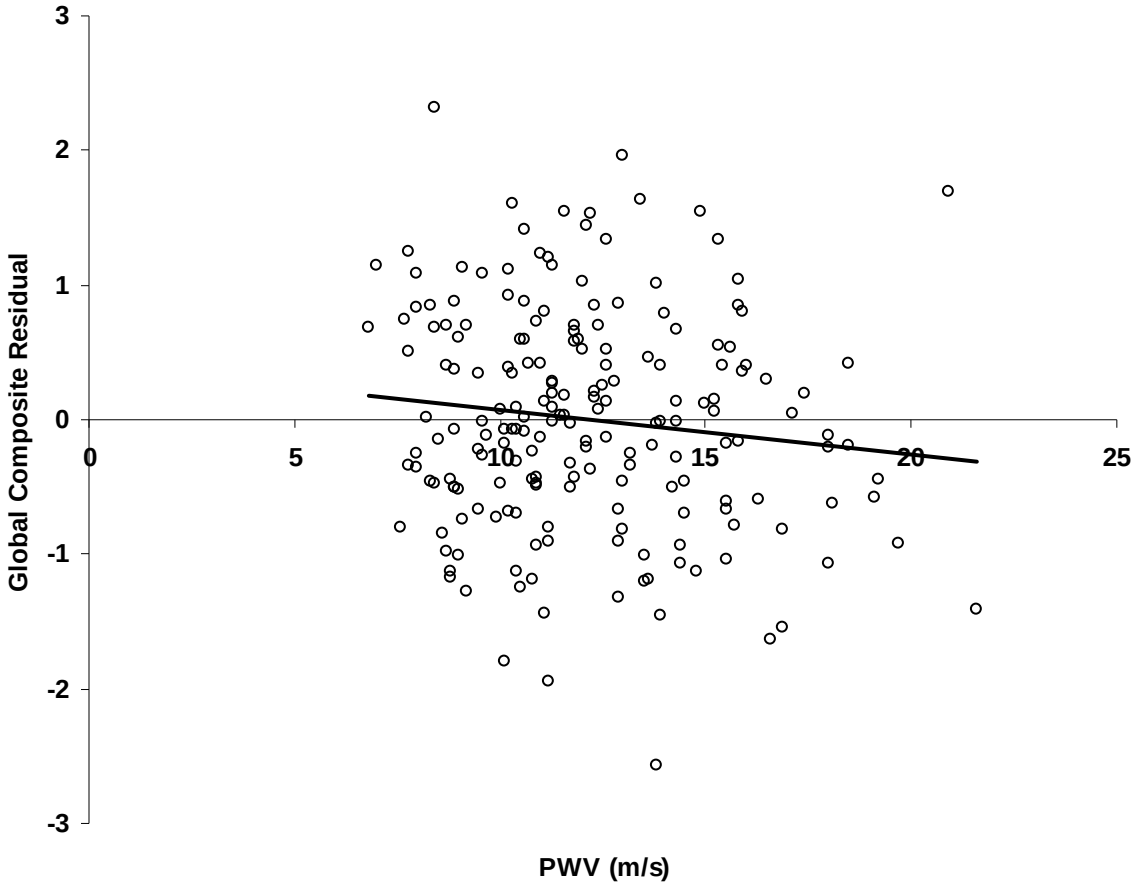

Figure 3.4. Relationship between PWV and Global Composite residuals for individuals over 69 years of age. Adjusted for age, education, sex, ethnicity, heart rate, height, weight, MAP

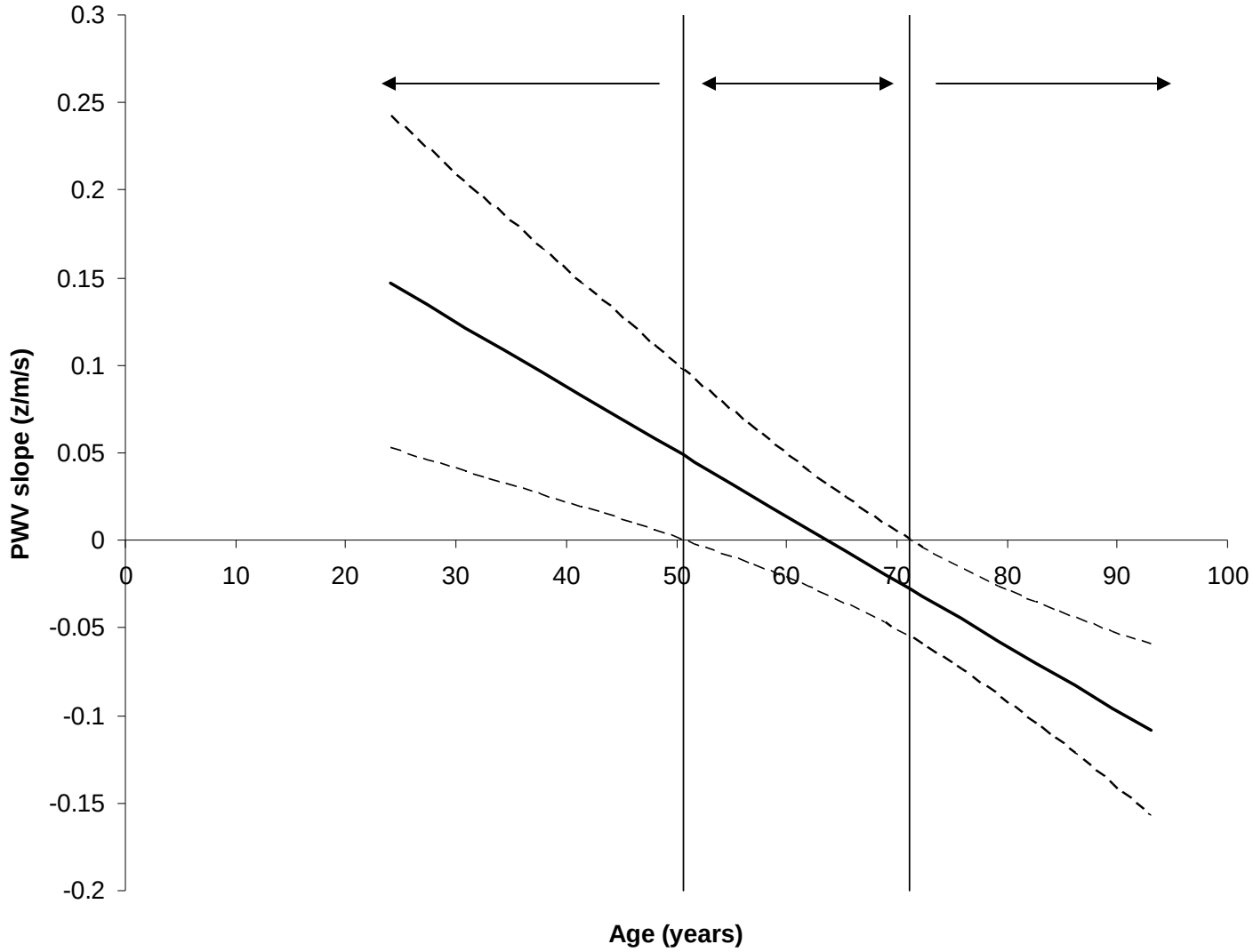

Figure 3.5. PWV slopes and 95% confidence intervals by age estimated using the Johnson-Neyman technique for the Global Composite (basic model).

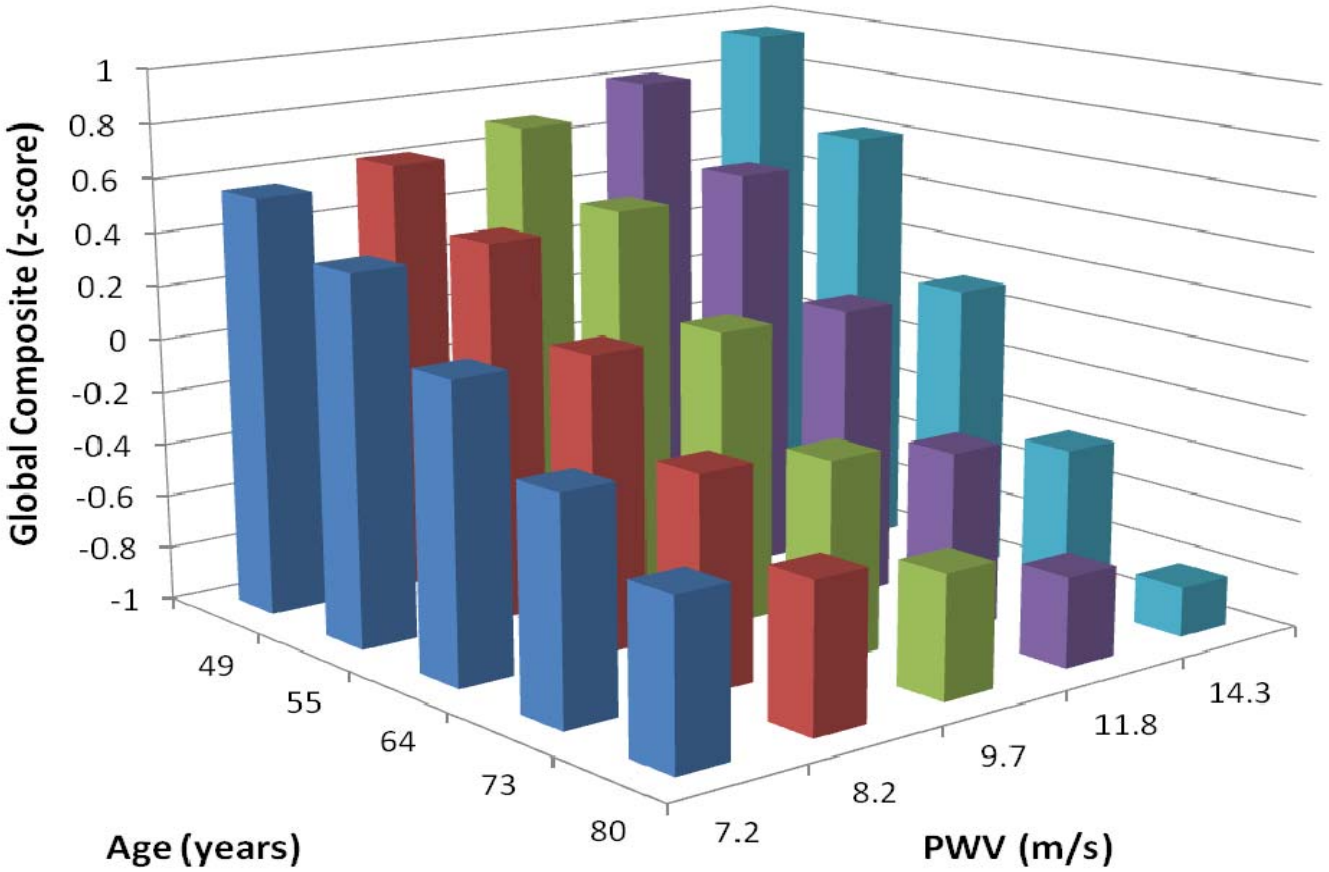

Figure 3.6. Association between PWV and the Global Composite, as modified by age.

extended model. Since positive relations between PWV and cognition were obtained under the age of 51, other indices of arterial stiffness were examined to see if this same pattern of results would be obtained.

In an additional analysis we examined the association between the PWV × age interaction and the individual tests within the Working Memory composite, in order to determine if the PWV × age interaction was associated with any of the individual tests within this composite. The PWV × age interaction was related to Letter-Number Sequencing ($p= 0.03$) and COWA ($p= 0.02$), but not Digit Span Forward ($p= 0.76$) or Digit Span Backward (0.75).

3.5. Other Indices of Arterial Stiffness

Table 3.6 shows statistical main effects of the various measures of arterial stiffness, including PWV, in relation to cognitive outcome measures. Other than PWV, none of the other measures of arterial stiffness were related to the Global composite. The only significant main effects observed were for AIx (Scanning and Tracking) and aPP (VSOM).

Table 3.7 shows results for the arterial stiffness × age interaction. Similar to results for the main effects, *other than PWV*, none of the arterial stiffness measures interacted significantly with age. The only significant results were for bPP × age (Working Memory and Executive Function), and aPP × age (Executive Function). Given that none of the arterial stiffness measures satisfied the requirements for inclusion in analyses (i.e. none were significantly related to the Global Composite), the analyses

Table 3.6. Main effects - Regression coefficients (b) and standard errors (se) expressing the association between measures of arterial stiffness and cognitive functioning

		Arterial Stiffness Measure				
Test		PWV	AIx	AP	bPP	aPP
Global	b	-0.029*	0.003	-0.003	-0.004	-0.005
	se	0.014	0.004	0.006	0.003	0.003
Verbal Memory	b	-0.022	-0.000	-0.003	0.001	-0.002
	se	0.017	0.005	0.007	0.004	0.004
Visual-Spatial Organization and Memory	b	-0.021	0.002	-0.007	-0.004	-0.008*
	se	0.015	0.004	0.006	0.003	0.003
Scanning and Tracking	b	-0.033*	0.008*	0.005	-0.006†	-0.002
	se	0.014	0.004	0.006	0.003	0.003
Working Memory	b	-0.026	-0.002	-0.008	-0.004	-0.004
	se	0.018	0.005	0.007	0.004	0.004
Similarities	b	-0.007	0.002	0.007	0.005	0.003
	se	0.017	0.005	0.007	0.004	0.004
Executive Function	b	-0.033*	0.005	0.002	-0.003	-0.002
	se	0.017	0.004	0.007	0.004	0.004

†p< 0.10; *p< 0.05

model = [arterial stiffness variable], age, education, sex, ethnicity, height, weight, heart rate, brachial MAP

PWV: pulse wave velocity
AIx: augmentation idex
AP: augmentation pressure
bPP: brachial pulse pressure
aPP: aortic pulse pressure

Table 3.7. Arterial stiffness × age interactions - Regression coefficients (b) and standard errors (se) for the arterial stiffness × age interaction.

		Arterial Stiffness Measure				
Test		PWV	AIx	AP	bPP	aPP
Global	b	-0.0037***	0.0001	-0.0003	-0.0003	-0.0003
	se	0.0010	0.0002	0.0003	0.0002	0.0002
Verbal Memory	b	-0.0037**	0.0000	-0.0001	0.0000	-0.0001
	se	0.0012	0.0003	0.0004	0.0002	0.0002
Visual-Spatial Organization and Memory	b	-0.0039***	0.0002	-0.0000	-0.0002	-0.0001
	se	0.0010	0.0003	0.0003	0.0002	0.0002
Scanning and Tracking	b	0.0027**	0.0000	-0.0005	-0.0003	-0.0003†
nh	se	0.0010	0.0002	0.0003	0.0002	0.0002
Working Memory	b	-0.0018	0.0001	-0.0003	**-0.0005***	-0.0003
	se	0.0012	0.0003	0.0004	**0.0002**	0.0002
Similarities	b	-0.0028*	-0.0001	-0.0002	-0.0002	-0.0002
	se	0.0012	0.0003	0.0004	0.0002	0.0002
Executive Function	b	-0.0038**	-0.0001	-0.0006	**-0.0005***	**0.0005***
	se	0.0011	0.0003	0.0003	**0.0002**	**0.0002**

†p< 0.10; *p< 0.05; **p< 0.01; ***p<0.001

model = [arterial stiffness variable], age, education, sex, ethnicity, height, weight, heart rate, brachial MAP

PWV: pulse wave velocity
AIx: augmentation index
AP: augmentation pressure
bPP: brachial pulse pressure
aPP: aortic pulse pressure

involving the full path model (discussed in the following section) include only PWV as a measure of arterial stiffness.

3.6. Mediational Analyses

While path analysis does not establish causal associations between or among variables, the term "effect" is used here to be consistent with its statistical use and the vocabulary of path analysis.

Figure 3.7 shows individual component paths for the basic model with the Global Composite as the outcome. From these component paths, the total conditional direct and indirect effects may be calculated. The direct effect conditional on *APOE* genotype is given by the following combination of the c_1' (diabetes → Global Composite) path and the c_3' path (Diabetes × *APOE* → Global Composite) paths: conditional direct effect = $c_1' + c_3'$ [*APOE* genotype]. That is, the direct effect of diabetes is conditional on *APOE* genotype. For example, for the *APOE*-ε4 carriers, the direct effect of diabetes would be (within rounding error): -0.0558 + (-0.4975)(1) = -0.5533.

The conditional indirect effect is calculated in a similar fashion. However, the indirect effect is conditional on both *APOE* genotype and age, and is given by: [$a_1 + a_3$ (*APOE*)][$b_1 + b_3$ (age)]. As an example, the indirect effect of diabetes on the Global Composite (through PWV) for a 73-year-old *APOE*-ε4 carrier is (within rounding error): [1.3281 + 2.0285(1)][0.2798 + (-0.0041)(73)] = -0.0655.

The total effect would be the combination of the direct and indirect effects. For the examples given above, the total effect would be: -0.5533 + (-0.0655) = -0.619.

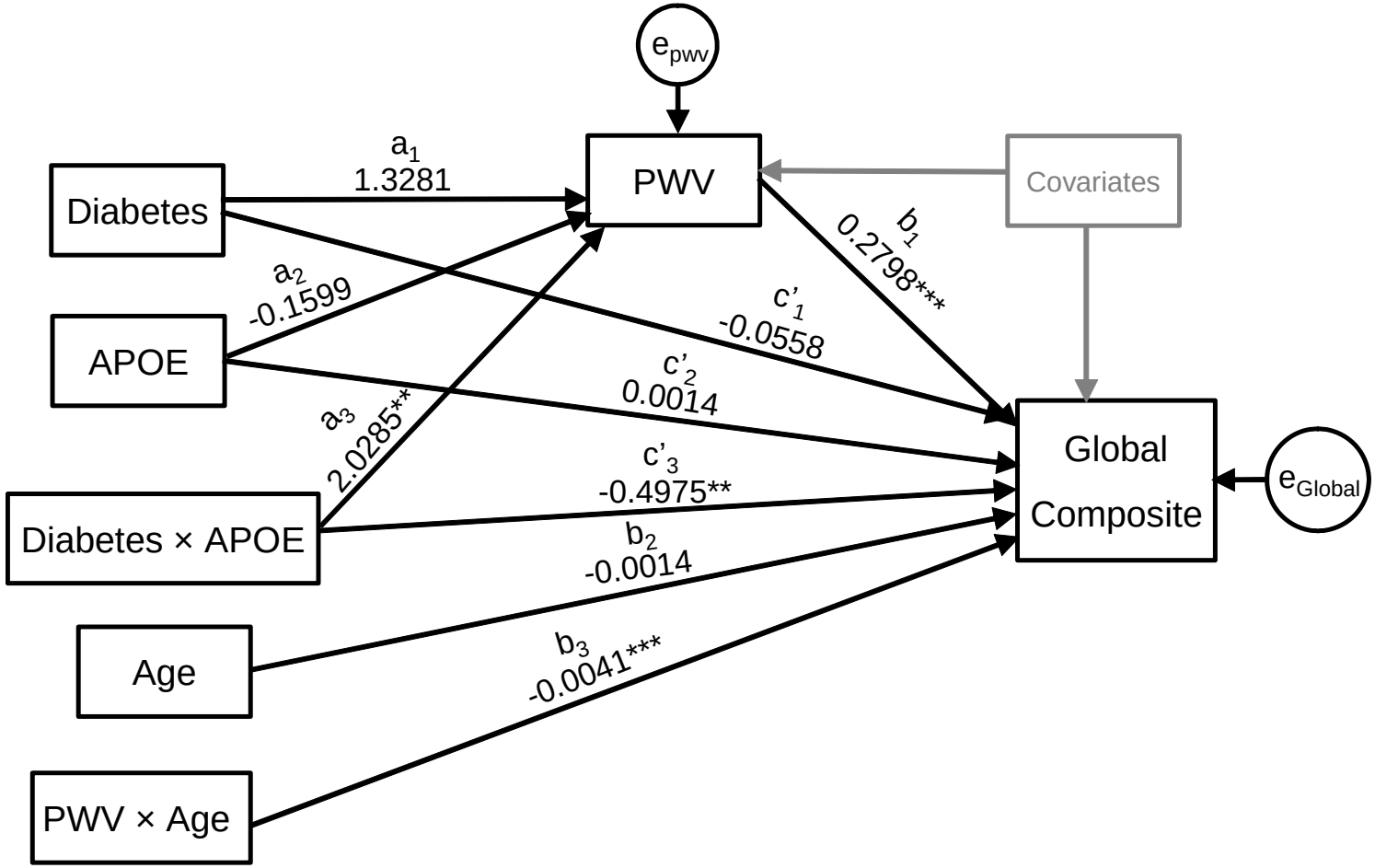

Figure 3.7. Simplified path model used to assess the conditional (moderated by age and APOE) indirect effect of diabetes on cognitive function through PWV. Hayes (2012) model 22

Conditional indirect effect of *diabetes* on *cognition* through *PWV* = $(a_1 + a_3[APOE])\ (b_1 + b_3[age])$
Conditional direct effect of *diabetes* on *cognition* = $c'_1 + c'_3[APOE]$

Therefore, a 73-year-old diabetic *APOE*-ε4 carrier would be expected to perform 0.619 SD below the mean on the Global Composite.

Component paths relevant to the direct and indirect effects for other cognitive outcomes are given for the basic model in Table 3.8 and for the extended model in Table 3.9. This information is given for the reader's information; the direct and indirect effects are calculated and provided in Tables 3.10-3.13 (discussed below).

Conditional direct effects (moderated by *APOE* genotype) and conditional indirect effects (moderated by *APOE* genotype and age) for the basic model are given in Tables 3.10 and 3.11. As can be seen in Table 3.10, none of the direct effects of diabetes on cognitive function were statistically significant for the no-*APOE*-ε4 group. Conversely, direct effects of diabetes on cognitive function for the *APOE*-ε4 group were statistically significant for all cognitive outcome variables (Table 3.11)

This same pattern of results was observed with adjustment for the extended covariate set (Tables 3.12 and 3.13). However, the direct effect of diabetes on VSOM no longer remained statistically significant for the *APOE*-ε4 group. Effects remained for the Global, Verbal Memory, Visual-Spatial Organization/Memory, Working Memory, and Executive function composites, as well as for Similarities.

Conditional indirect effects of diabetes through PWV (effects moderated by age as well as *APOE*) on cognitive function were positive for the younger individuals, and negative for older individuals. This was true for both the basic (Tables 3.10 and 3.11) and extended (Tables 3.12 and 3.13) models.

Although positive indirect effects between diabetes and cognitive function were observed for the younger individuals, it is important to note that the net or total effect

Table 3.8. Basic model component path coefficients (b) and standard errors (se) of the direct effects[1] of diabetes on cognitive function and conditional indirect effects[2] of diabetes on cognitive function through PWV.

Cognitive Outcome		Direct Effect Component Path[3]		Indirect Effect Component Path[4]			
		c_1'	c_3'	a_1	a_3	b_1	b_3
Global	b	-0.0558	-0.4975**	1.3281***	2.0285**	0.2798***	-0.0041***
	se	0.1043	0.1789	0.3734	0.6431	0.0717	0.0010
Verbal Memory	b	-0.0024	-0.4983*	1.3205***	2.0346**	0.2797**	-0.0041***
	se	0.1262	0.2165	0.3730	0.6427	0.0868	0.0012
VSOM	b	-0.1145	-0.2290	1.3205***	2.0346**	0.2881***	-0.0042***
	se	0.1132	0.1941	0.3730	0.6427	0.0778	0.0011
Scanning & Tracking	b	0.0501	-0.4568*	1.3205***	2.0346**	0.1858*	-0.0029**
	se	0.1063	0.1823	0.3730	0.6427	0.0731	0.0010
Working Memory	b	-0.0903	-0.4993*	1.3205***	2.0346**	0.1516	-0.0023
	se	0.1326	0.2275	0.3730	0.6427	0.0912	0.0012
Similarities	b	0.0034	-0.6408**	1.3281***	2.0285**	0.2423**	-0.0033**
	se	0.1270	0.2177	0.3734	0.6431	0.0873	0.0012
Executive Function	b	-0.1359	-0.3563	1.3205***	2.0346**	0.2807***	-0.0042***
	se	0.1233	0.2115	0.3730	0.6427	0.0848	0.0011

***p< 0.001; **p< 0.01; *p<0.05

covariates = age, education, gender, ethnicity, heart rate, height, weight, MAP

Conditional indirect effect of *diabetes* on *cognition* through *PWV* = $[a_1 + a_3(APOE)][b_1 + b_3(age)]$
Conditional direct effect of *diabetes* on *cognition* = $c'_1 + c'_3(APOE)$

[1]conditional on *APOE*; not mediated by PWV
[2]conditional on *APOE* and age; mediated by PWV
[3]direct effect component path: c'_1 = diabetes → cognitive variable; c'_3 = diabetes × *APOE* → cognitive variable
[4]indirect effect component path: a_1 = diabetes → PWV; a_3 = diabetes × *APOE* → PWV; b_1 = PWV → cognitive variable; b_1 = PWV × age → cognitive variable

Table 3.9. Extended model component path coefficients (b) and standard errors (se) of the direct effects[1] of diabetes on cognitive function and conditional indirect effects[2] of diabetes on cognitive function through PWV.

Cognitive Outcome		Direct Effect Component Path		Indirect Effect Component Path			
		c_1'	c_3'	a_1	a_3	b_1	b_3
Global	b	-0.0276	-0.4420*	1.1598**	2.1487***	0.2552***	-0.0038***
	se	0.1040	0.1777	0.3633	0.6218	0.0714	0.0010
Verbal Memory	b	0.0188	-0.4812*	1.1487**	2.1542***	0.2684**	-0.0039***
	se	0.1274	0.2179	0.3630	0.6216	0.0875	0.0012
VSOM	b	-0.0976	-0.1862	1.1487**	2.1542***	0.2627***	-0.0038***
	se	0.1133	0.1938	0.3630	0.6216	0.0778	0.0011
Scanning & Tracking	b	0.0729	-0.3796*	1.1487**	2.1542***	0.1504*	-0.0025*
	se	0.1046	0.1789	0.3630	0.6216	0.0718	0.0010
Working Memory	b	-0.0552	-0.4509*	1.1487**	2.1542***	0.1471	-0.0022
	se	0.1334	0.2282	0.3630	0.6216	0.0916	0.0012
Similarities	b	0.0211	-0.6041**	1.1598**	2.1487***	0.2240*	-0.0030*
	se	0.1278	0.2184	0.3633	0.6218	0.0877	0.0012
Executive Function	b	-0.0985	-0.2822	1.1487**	2.1542***	0.2600**	-0.0039***
	se	0.1226	0.2094	0.3630	0.6216	0.0829	0.0011

***p< 0.001; **p< 0.01; *p<0.05

covariates = age, education, gender, ethnicity, heart rate, height, weight, MAP, alcohol consumption, triglycerides, CES-D, CVD

Conditional indirect effect of *diabetes* on *cognition* through *PWV* = $[a_1 + a_3(APOE)][b_1 + b_3(age)]$
Conditional direct effect of *diabetes* on *cognition* = $c'_1 + c'_3(APOE)$

[1]conditional on *APOE*; not mediated by PWV
[2]conditional on *APOE* and age; mediated by PWV

Table 3.10. Results for the no *APOE*-ε4 group, basic model. Path coefficients (b) and standard errors (se) representing conditional direct effects[1] of diabetes on cognitive function and conditional indirect effects[2] of diabetes on cognitive function through PWV.

		Conditional Direct Effect	Conditional Indirect Effect at Age Values				
Cognitive Outcome			49 years	55 years	64 years	73 years	80 years
Global	b	-0.056	0.104*	0.071*	0.022	-0.027	-0.066*
	se	0.104	0.054	0.041	0.025	0.022	0.031
Verbal Memory	b	-0.002	0.107*	0.075*	0.027	-0.021	-0.059*
	se	0.126	0.056	0.043	0.027	0.026	0.036
VSOM	b	-0.115	0.110*	0.077*	0.027	-0.023	-0.061*
	se	0.113	0.060	0.046	0.029	0.024	0.032
Scanning & Tracking	b	0.050	0.056	0.033	-0.002	-0.037*	-0.064*
	se	0.106	0.042	0.033	0.024	0.021	0.027
Working Memory	b	-0.090	0.054	0.037	0.010	-0.017	-0.038
	se	0.133	0.054	0.043	0.030	0.025	0.029
Similarities	b	0.003	0.108*	0.082*	0.043	0.004	-0.027
	se	0.127	0.062	0.049	0.032	0.025	0.031
Executive Function	b	-0.136	0.101*	0.068*	0.018	-0.031	-0.070*
	se	0.123	0.053	0.041	0.027	0.023	0.032

***p< 0.001; **p< 0.01; *p<0.05; †p<0.06

covariates = age, education, gender, ethnicity, heart rate, height, weight, MAP

[1]conditional on *APOE*; not mediated by PWV
[2]conditional on *APOE* and age; mediated by PWV

Table 3.11. Results for the *APOE*-ε4 group, basic model. Path coefficients (b) and standard errors (se) representing direct effects[1] of diabetes on cognitive function and conditional indirect effects[2] of diabetes on cognitive function through PWV

		Conditional Direct Effect	Conditional Indirect Effect at Age Values				
Cognitive Outcome			49 years	55 years	64 years	73 years	80 years
Global	b	-0.553***	0.262*	0.179*	0.055	-0.069	-0.166*
	se	0.158	0.114	0.090	0.060	0.052	0.067
Verbal Memory	b	-0.501**	0.272*	0.191*	0.068	-0.054	-0.149*
	se	0.191	0.123	0.098	0.068	0.061	0.077
VSOM	b	-0.343*	0.279*	0.195*	0.069	-0.057	-0.155*
	se	0.172	0.129	0.102	0.069	0.059	0.075
Scanning & Tracking	b	-0.407*	0.142	0.084	-0.005	-0.093*	-0.162*
	se	0.161	0.099	0.081	0.059	0.053	0.062
Working Memory	b	-0.590**	0.138	0.092	0.025	-0.043	-0.096
	se	0.201	0.128	0.105	0.074	0.061	0.068
Similarities	b	-0.637***	0.274*	0.208*	0.109	0.009	-0.068
	se	0.192	0.131	0.106	0.074	0.061	0.071
Executive Function	b	-0.492**	0.256*	0.172*	0.046	-0.080	-0.177*
	se	0.187	0.115	0.092	0.064	0.056	0.068

***p< 0.001; **p< 0.01; *p<0.05; †p<0.06

covariates = age, education, gender, ethnicity, heart rate, height, weight, MAP

[1]conditional on *APOE*; not mediated by PWV
[2]conditional on *APOE* and age; mediated by PWV

(i.e.. the sum of the direct and indirect effect) of diabetes is either close to zero (as in the no *APOE*-ε4 group) or negative (as in the *APOE*-ε4 group), consistent with analyses discussed previously.

3.7. Secondary Analyses

A recent study (Schillaci et al., 2007) showed that a higher venticular contractility rate is a main determinant of PWV in younger individuals. In the current data, ejection duration, a measure of ventricular contractility rate, was modestly correlated with PWV in the youngest (age < 59) and middle (59-69) age tertiles (r= -0.22 and -0.28, respectively). Therefore, in secondary analyses, we additionally adjusted PWV for ejection duration and the ejection duration × age interaction. The pattern of results with these additional variables in the model was the same as that outlined above.

Previous research has also suggested that although PWV may be a useful measure of arterial stiffness in older individuals, it may not be a reliable measure of arterial stiffness in younger individuals, with AIx being the preferred measure for individuals under 50 years of age (McEniery, Yasmin, Hall, et al., 2005). Therefore, we combined PWV and AIx into a single arterial stiffness "composite" variable by standardizing each measure and using standardized AIx for individuals under 50 years of age, and using standardized PWV for individuals 50 and older. The resulting observed relationship between the arterial stiffness composite, age, and the Global Composite is shown in Figure 3.8. For older individuals, higher arterial stiffness was related to lower cognitive function ($p < 0.05$). However, no association was observed for younger individuals ($p > 0.05$). When the arterial stiffness variable was used in the overall path model, indirect

Table 3.12. Results for the no *APOE*-ε4 group, extended model. Path coefficients (b) and standard errors (se) representing direct effects[1] of diabetes on cognitive function and conditional indirect effects[2] of diabetes on cognitive function through PWV.

		Conditional Direct Effect	Conditional Indirect Effect at Age Values				
Cognitive Outcome			49 years	55 years	64 years	73 years	80 years
Global	b	-0.028	0.081*	0.054*	0.015	-0.025	-0.056*
	se	0.104	0.049	0.036	0.022	0.020	0.030
Verbal Memory	b	0.019	0.087*	0.060*	0.019	-0.022	-0.054*
	se	0.127	0.052	0.040	0.025	0.025	0.035
VSOM	b	-0.098	0.086*	0.059*	0.019	-0.020	-0.051*
	se	0.113	0.054	0.041	0.026	0.021	0.029
Scanning & Tracking	b	0.073	0.035	0.018	-0.008	-0.033	-0.053*
	se	0.105	0.035	0.028	0.021	0.020	0.025
Working Memory	b	-0.055	0.047	0.032	0.009	-0.013	-0.031
	se	0.133	0.049	0.040	0.028	0.023	0.027
Similarities	b	0.021	0.089*	0.068*	0.036	0.005	-0.020
	se	0.128	0.056	0.044	0.029	0.022	0.028
Executive Function	b	-0.099	0.079*	0.053*	0.013	-0.027	-0.057*
	se	0.123	0.046	0.035	0.022	0.022	0.031

***p< 0.001; **p< 0.01; *p<0.05; †p<0.06

covariates = age, education, gender, ethnicity, heart rate, height, weight, MAP, alcohol consumption, triglycerides, CES-D, CVD

[1]conditional on *APOE*; not mediated by PWV
[2]conditional on *APOE* and age; mediated by PWV

Table 3.13. Results for the *APOE*-ε4 group, extended model. Path coefficients (b) and standard errors (se) representing direct effects[1] of diabetes on cognitive function and conditional indirect effects[2] of diabetes on cognitive function through PWV.

		Conditional Direct Effect	Conditional Indirect Effect at Age Values				
Cognitive Outcome			49 years	55 years	64 years	73 years	80 years
Global	b	-0.470**	0.230*	0.155*	0.042	-0.071	-0.159*
	se	0.158	0.109	0.087	0.060	0.052	0.064
Verbal Memory	b	-0.462*	0.249*	0.171*	0.054	-0.063	-0.154*
	se	0.194	0.117	0.094	0.067	0.062	0.077
VSOM	b	-0.284	0.246*	0.170	0.056	-0.059	-0.148*
	se	0.173	0.125	0.100	0.068	0.057	0.070
Scanning & Tracking	b	-0.307*	0.099	0.051	-0.022	-0.095*	-0.152*
	se	0.159	0.096	0.079	0.058	0.052	0.060
Working Memory	b	-0.506*	0.134	0.091	0.026	-0.039	-0.089
	se	0.203	0.129	0.105	0.075	0.061	0.068
Similarities	b	-0.583**	0.253*	0.193*	0.104	0.014	-0.056
	se	0.194	0.128	0.103	0.073	0.061	0.072
Executive Function	b	-0.381*	0.221*	0.147*	0.037	-0.074	-0.160*
	se	0.185	0.106	0.085	0.060	0.053	0.065

***p< 0.001; **p< 0.01; *p<0.05

covariates = age, education, gender, ethnicity, heart rate, height, weight, MAP, alcohol consumption, triglycerides, CES-D, CVD

[1]conditional on *APOE*; not mediated by PWV
[2]conditional on *APOE* and age; mediated by PWV

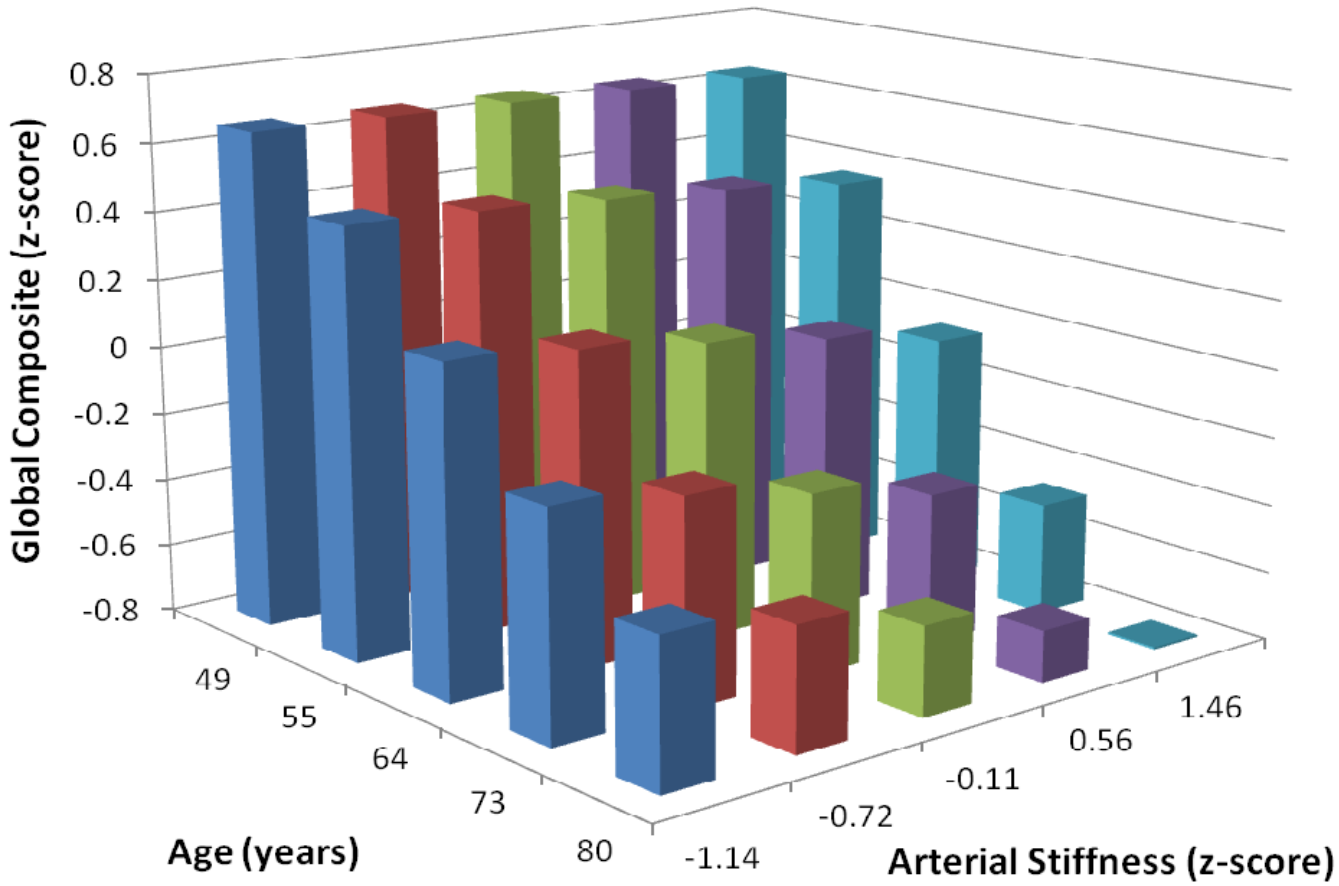

Figure 3.8. Association between the arterial stiffness composite and the Global Composite, as modified by age.

effects from diabetes through PWV to cognition were observed for older individuals only. All significant indirect effects were in a negative direction.

3.8. Summary of Results

Significant interactions were observed between diabetes and *APOE* such that the diabetic *APOE*-ε4 carriers exhibited the lowest performance, compared with all other groups. PWV × age interactions were also observed such that the most negative PWV slopes in relation to cognitive performance were observed for the oldest individuals. However, contrary to expectation, this trend was in the opposite direction for younger individuals (under approximately 50 years of age).

For the overall path analysis, significant conditional direct associations between diabetes and cognitive outcomes were observed for the *APOE*-ε4 carriers only. Conditional indirect associations between diabetes and cognitive outcomes were observed for younger (under ~50 years of age) and older (over ~70-80 years of age). However these effects were in opposite directions, with a positive indirect effect in younger individuals, and a negative indirect effect in younger individuals. These effects were also larger in the *APOE*-ε4 carriers. Other indices of arterial stiffness, augmentation index, augmentation pressure, brachial pulse pressure, and central pulse pressure, were examined with respect to direct and indirect effects, but this examination did not clarify relations between arterial stiffness and cognitive function because there were many fewer significant indirect effects for these variables. While the complex indirect effects of PWV are of theoretical interest, the magnitude of these effects was relatively small.

4. DISCUSSION

4.1. Summary of Most Pertinent Findings

Previous studies have examined the association between type 2 diabetes and cognitive function (Kodl & Seaquist, 2008); diabetes and PWV (Cameron & Cruikshank, 2007); and PWV and cognitive function (Elias et al., 2009; Waldstein et al., 2008). The current study builds on this research and examines the associations between diabetes, PWV, and cognitive function simultaneously. The major finding in the current study is that PWV (a gold standard index of arterial stiffness) partially mediates the association between diabetes and cognitive function. Although, as expected, direct associations between diabetes and cognitive function were observed with indirect effects included in the model. With respect to relative effect sizes, where these direct associations were observed (i.e. in the *APOE*-ε4 group), they were approximately three times the magnitude of the indirect effects. Additionally, this diabetes → PWV → cognitive function association is modified by age and *APOE* genotype. In the following sections, we elaborate on the specifics of these findings and discuss each of them. First, we will discuss findings related to *APOE* genotype as an effect modifier of the relationship between diabetes and cognitive function. Then, we turn to age as an effect modifier of the relationship between PWV and cognitive function. Finally, we discuss how these findings are inter-related in the context of a path model.

4.2. Diabetes, APOE Genotype, and Cognitive Function

APOE was found to be an effect modifier of the association between diabetes and cognitive function. In fact, deficits in cognitive performance were observed only for those with diabetes and at least one *APOE*- ε4 allele. This finding is consistent with a previous study using data from Wave 6 of the MSLS (Dore et al., 2009). Previous investigations have also found *APOE* genotype to modify the associations of other cardiovascular risk factors on cognitive function. *APOE*-ε4 has been shown to modify the association of homocysteine with cognitive function (Elias et al., 2008); peripheral vascular disease, carotid atherosclerosis, and diabetes with cognitive decline (Haan, Shemanski, Jagust, et al., 1999); and diabetes with dementia (Irie, Fitzpatrick, Lopez, et al., 2008; Peila, Rodriguez, & Launer, 2002).

There are several mechanisms that may explain this association. Hyperglycemia in the cerebral vasculature is related to endothelial dysfunction (Messier & Gagnon, 2009). The *APOE* gene codes for the apoE protein, which is a cholesterol transport protein produced mainly in the liver and brain (Mahley, 1988). ApoE plays an important role not only in cholesterol transport, but also in amyloid-β (Aβ) clearance, neuronal repair, and mediation of Aβ-related neurotoxicity (Bu, 2009). The apoE-ε4 isoform in deficient in all of these areas, compared with apoE-ε2 and apoE-ε3 (Bu, 2009). Additionally, the *APOE*-ε4 allele has been associated with increased cerebral amyloid angiopathy (CAA; Thal et al., 2010), as well as increased white matter hyperintensities and smaller brain volume in those with cerebrovascular disease (Decarli, Reed, Miller et al., 1999). This enhanced Aβ deposition in the cerebral vasculature observed in *APOE*-ε4 carriers may interact synergystically with the increased vascular pathology (Puri,

Kataoka, Uno, & Nicholls, 2012) and increased white matter hyperintensities (Novak et al., 2006) observed in diabetic individuals, ultimately resulting in lower cognitive function . Thus, diabetes is related to increased vascular pathology, and possession of one or more *APOE*-ε4 alleles may either increase the degree of this pathology, or exacerbate any effects of this pathology on cognitive performance.

Clinically, it may be important to treat diabetic *APOE*-ε4 carriers differently than diabetic *APOE*-ε4 non-carriers. That is, diabetic *APOE*-ε4 carriers may need more aggressive treatment with glucose lowering medications. CVD risk factors related to diabetes, including PWV, may be important treatment targets to minimize cognitive decrement in these individuals. Previous research has determined that treatment with antidiabetic agents improves both cognitive function (Ryan et al., 2006) and endothelial function (Mather, Verma, & Anderson, 2001). More recently, Lim et al. (2011) found that treatment with a low-calorie liquid diet reversed pancreatic pathology in diabetic individuals, resulting in normalized glucose values after one week. Although this research needs to be replicated in larger samples, it would be interesting to see whether this same protocol would improve arterial stiffness and cognitive performance. These considerations may be especially important for older *APOE*-ε4 carriers.

We now turn to the next major association in the current study: the association between PWV and cognitive function as modified by age.

4.3. PWV, Age, and Cognitive Function

An inverse association between PWV and cognitive function was observed in older individuals. That is, the poorest performance was observed in the oldest individuals

with the highest PWV. This is consistent with previous studies of PWV and cognitive function (Elias et al., 2009) and longitudinal cognitive decline (Waldstein et al., 2008). However, a positive association was observed between PWV and cognitive function for younger individuals. This is an unexpected and novel finding and has not been addressed in the literature.

There could be several reasons why this observation is unique to the current study. First, studies of CVD risk factors, including PWV, have focused on older individuals (e.g. Fujiwara et al., 2005; Benetos et al., 2012), most likely due to the fact that arterial stiffness develops over time (Greenwald, 2007), and therefore is much more common in older adults (Reference Values for Arterial Stiffness' Collaboration, 2010; Elias et al. 2011) and with increasing age beyond middle age. This emphasis on aging arteries is very possibly why the association between PWV and cognitive function has rarely been studied in younger individuals.

There are several possible explanations as to why PWV is positively related to cognitive function in younger individuals. One possibility is that the positive association between PWV and cognitive function for younger individuals may, like left ventricular hypertrophy (Gaasch & Zile, 2011), represent an initially adaptive result of vascular remodeling, which ultimately, but not initially, has adverse physiological consequences.

It is possible, however, that PWV is a reliable measure of arterial stiffness in older, but not younger, individuals. Consistent with this explanation, Schillaci et al. (2007) found PWV to be related to arterial stiffness in older individuals. However, in younger individuals, PWV was related to the speed of ventricular contraction, rather than arterial stiffness *per se*. The best index of ventricular contraction, although indirect,

available in the current data is ejection duration. Using this measure, we examined whether: 1) ejection duration is correlated with PWV in younger individuals, and 2) if positive associations between PWV and cognitive function in younger individuals are attenuated with adjustment for ejection duration. We found ejection duration to be modestly correlated with PWV in younger individuals; however, with adjustment for ejection duration, the pattern of results remained the same, i.e., PWV was related positively to cognitive function in younger individuals. Consequently, the ventricular contraction hypothesis as an explanation for the unexpected finding in younger subjects was rejected.

Some previous research has also suggested AIx to be a better measure of arterial stiffness in younger individuals, as compared with PWV (McEniery et al., 2005). When we substituted AIx for PWV as the arterial stiffness measure in younger individuals only, no association between arterial stiffness and cognitive function was observed. This is not an unexpected finding because of the low prevalence of arterial stiffness below the age of (Reference Values for Arterial Stiffness' Collaboration, 2010; Elias et al. 2011). However, it will be noted that AIx was also a poorer predictor of cognitive performance, compared with PWV, in the older subjects in this study.

These analyses do not fully address reasons for the positive association between PWV and cognitive function in younger individuals. Further study is needed examining structural vascular correlates of PWV in younger individuals.

4.4. From Diabetes to PWV to Cognitive Deficit

When the diabetes × *APOE* genotype and PWV × Age effects were combined in a meditational path model, similar results to those outlined above were obtained. Direct (non-mediated) associations between diabetes and cognitive function were observed for *APOE*-ε4 carriers only. Diabetic *APOE*-ε4 carriers performed approximately half a standard deviation below the mean on all cognitive measures. In addition to direct effects, indirect effects (through PWV) were observed for all cognitive outcomes, with the exception of the Working Memory composite.

In addition to being moderated by *APOE* genotype, these indirect effects were also moderated by age. For younger individuals, positive indirect associations were observed. As diabetes was consistently related positively to PWV, the sign of these indirect associations was determined by the PWV × age interaction. Therefore, for reasons discussed above, these positive associations should be interpreted with caution. When AIx was used as the measure of arterial stiffness in these individuals, indirect effects were observed for older individuals only. It should also be noted that even if these positive indirect effects in younger individuals are valid, the overall associations between diabetes and cognitive function variables were observed to be near zero (for the no-*APOE*-ε4 group) or negative (for the *APOE*-ε4 group).

Conversely, negative indirect effects were observed for older individuals. In these individuals, the associations between diabetes and cognitive function were partially mediated by PWV. This was true for all cognitive measures, with the exception of Working Memory and Similarities. This suggests that associations between diabetes and cognitive function are in part mediated by arterial stiffness. All of these indirect

associations were moderated by *APOE* genotype in addition to age. That is, all associations were magnified in those with at least one *APOE*-ε4 allele.

The association between diabetes and increased arterial stiffness is well-established (see Stehouwer et al., 2008 for review). Increased atherosclerotic plaque deposition, exacerbated by the increased inflammatory (i.e. immune) response characteristic of the diabetic state is one mechanism which leads to increased arterial stiffness. Chronic hyperglycemia results in the accelerated formation of advanced glycation endproducts (AGEs), promoting the formation of oxidized low density lipoproteins (LDL; Basta, Schmidt, & De Caterina, 2004), which is more atherogenic than normal LDL (Xu, He, & King, 2005). In addition, increased oxidative stress (increased production of reactive oxygen species), possibly due to increased AGE formation (Stitt, Jenkins, & Cooper, 2002) or resulting directly from chronic hyperglycemia (Brownlee, 2001), may decrease bioavailability of nitric oxide (a vasodilator) and activate the protein kinase C pathway, resulting in maintenance of a chronic inflammatory state (Jenkins, Hill, & Rowley, 2008). In addition to factors leading to increased atherosclerotic plaque deposition, diabetes is also associated with increased arterial calcification, further increasing arterial stiffness (Chen & Moe, 2003).

Higher levels of arterial stiffness, in turn, have been shown to relate to lowered levels of cognitive function (M. F. Elias, Robbins, et al., 2009), and more accelerated cognitive decline (Laurent, Cockroft, van Bortel,et al., 2006; Waldstein, Rice, Thayer, Najjar, Scuteri, & Zonderman, 2008; Benetos, Watfa, Hanon, et al., 2012; Watson, Sutton, Rosano, et al., 2011) in older, but not younger individuals. A recent study using data from wave 7 of the MSLS (M. F. Elias, Robbins, et al., 2009) found that arterial

stiffness, as indexed by PWV, interacted with age in relation to multiple cognitive domains. The combination of older age and higher PWV was found to be associated with the lowest level of cognitive performance, whereas lower age and PWV were associated with better performance. Similarly, in the Baltimore Longitudinal Study of Aging, Waldstein, Rice, Thayer, Najjar, Scuteri, & Zonderman (2008) found an interaction between PWV and cognitive change, such that individuals with the highest PWV exhibited the most pronounced rates of cognitive decline.

4.5. Cognitive Domains Associated with Diabetes

Although the specific cognitive tests used vary across studies, some generalizations can be made concerning the cognitive abilities related to diabetes. The most common finding is that diabetic subjects perform more poorly than nondiabetic subjects on tests of attention, verbal and non-verbal memory, and processing speed (Kodl & Seaquist, 2008; Roriz-Filho et al, 2009; van den Berg, Reijmer, & Biessels, 2009). There is less agreement on other cognitive abilities, but some investigators have reported that executive function (Kodl & Seaquist, 2008; Roriz-Filho et al, 2009), psychomotor speed, and complex motor function (Kodl & Seaquist, 2008) are lowered in diabetic individuals compared to non-diabetic individuals.

Consistent with these previous results, the current study suggests that diabetes is related to decrements in performance on a broad, rather than specific, range of cognitive abilities. Performance decrements in diabetic individuals were observed for all cognitive measures, with the exception of the VSOM and EF composites. Similarly, indirect associations (from diabetes to cognitive function through PWV) were observed for all

variables, with the exception of Working Memory and Similarities. Given that arterial stiffness involves arteries throughout the entire brain (Bornstein & Brown, 1991; Reitan & Wolfson, 1993), this finding, commonly found in studies of hypertension and cognition (Elias, Goodell, & Dore, 2012) is not unexpected.

The failure to see a relationship between the diabetes × *APOE* interaction term and executive function may be due to the fact that Trails B, but not COWA was related to the interaction term. Both Trails B and COWA are established indices of executive function. It is not clear why we obtained negative findings for COWA, Possibly this is related to the fact that our subjects are relatively highly educated and thus do well on measures of verbal fluency. Trails B is significantly less dependent on verbal skills (Rabbitt, 1998). It is possible that we would have found relationships between the diabetes × *APOE* interaction and EF had we used even more sensitive measures of executive function, which were not included in the MSLS test battery (e.g. the Stroop Color-Word test). These are speculative explanations subject to further research.

The present study also points to *APOE* genotype as an important consideration in studies of diabetes and cognitive functioning. In this study, decrements in cognitive performance were observed only for those diabetic individuals with an *APOE*-ε4 allele. Failure to consider this genetic variable may lead to under-estimation of the magnitude of association between diabetes and cognitive abilities. *APOE* genotype plays a role in repair of damaged neuronal structures; it has been argued that repair is slowed in persons carrying the *APOE*-ε4 allele (Horsburgh, McCarron, White, & Nicoll, 2005). The proportion of individuals with *APOE*-e4 genotype may differ among studies, particularly where sample size is small.

This may account for inconsistent findings in previous studies of diabetes and cognitive function where data on *APOE* genotype are not available. While there is a literature on other risk factors for cardiovascular disease and cognitive function, recent literature searches indicate that there have been no studies in other laboratories that have examined *APOE* in relation to diabetes.

4.6. Cognitive Domains Associated with PWV

We find that, like diabetes, PWV is associated with multiple cognitive domains. The PWV × age interaction was significant for all cognitive composites, with the exception of Working Memory. Data on the cognitive domains associated with PWV are limited. One major reason for this is that many of the studies of PWV and cognitive function use the MMSE or Modified MMSE as the sole measure of cognitive performance (Zhong, 2011). Of the studies using multiple tests of cognitive function, associations have been found between PWV and tests of: psychomotor and perceptual speed (Watson et al., 2011) and executive function (Poels et al., 2007; Muller et al., 2008). However, the results of these studies are made unclear by the fact that these studies did not examine interactions between PWV and age. Of the previous studies from other research groups, only one (Waldstein et al., 2008) included the PWV × age interaction, in relation to cognitive decline. PWV was found to be related to decline in verbal and nonverbal memory. Although far from being clear, the current literature suggests that, like diabetes, PWV is related to multiple cognitive domains. Further study using a variety of tests is necessary to determine specific cognitive domains related to PWV.

Although the APOE × age interaction term was not related to the Working Memory composite, it seems clear that this interaction term was related to critical and important indices of working memory. We speculate that that Digit Span Forward and Digit Span Back were not related to the interaction term, as they are not difficult tasks for highly performing individuals.

4.7. Limitations of the Current Study

The limitations of the current study should be noted. 1) The cross-sectional nature of this study does not allow us to measure decline in cognitive function over time. 2) Given the cross-sectional design, duration of diabetes could not be measured objectively, other than by self-report. Self-report of duration of diabetes is not a reliable measure because it only provides information on the time of diagnosis of diabetes, not when these disease processes first began. That is, an individual may be diabetic for a period of time before this condition is diagnosed. 3) The sample size was too small to allow examination of associations between diabetes and cognitive function in individuals with one vs. two *APOE*-ε4 alleles. This limitation is generally true of most studies of cardiovascular disease risk factors to date. 4) A1C, a recently emphasized index of diabetes, was not available to confirm the diagnosis of diabetes. However, while an A1C level greater than or equal to 6.5 has been adopted both nationally (American Diabetes Association, 2012b) and internationally (World Health Organization, 2011) into diagnostic criteria for diabetes, some debate still exists regarding the clinical utility of this measure (Hare, Shaw, & Zimmet, 2012). 5) It was not possible to adjust for antidiabetic medications in analyses with diabetes, as the majority of diabetic participants

were taking antidiabetic (90.5%) medications. This high percentage of treatment is related to the fact that once diabetes and hypertension are diagnosed in a longitudinal study, it is not ethically permissible to deny diabetic or hypertensive patients treatment.. The MSLS study protocol requires all participants to be referred for treatment following a wave of the study in which the likelihood of a disease process has been established. Due to the increased awareness and aggressive treatment of diabetes, this is true of most population-based longitudinal samples (Elias et al., 2004).

4.8. Strengths of the Current Study

The current study has several major strengths. First, it is the first to examine the meditational role of PWV in the association between diabetes and cognitive function. Second, it is one of the few studies to examine a wide range of ages thus leading to the finding that PWV does not relate to cognition in the same way in younger and older individuals. Third, many previous studies use patients with diagnosed diabetes and or persons being treated for diabetes in clinics. The current sample used comprises community-dwelling as compared to patients attending clinics and hospitals with a diagnosis of diabetes. Therefore, the results may better generalize to the general population. Fourth, the battery of cognitive tests is very likely the largest battery in use in NIH-sponsored studies of cardiovascular disease and cognition. Further, the cognitive measures were subject to factor analysis so that we were examining domains of functioning as compared to individual specific abilities measured by individual clinical tests. Sixth, the current study utilizes newer statistical methods (Hayes, 2012) to assess interactions between continuous variables and mediation moderated by continuous

variables. These methods have the advantage of not using arbitrary cutpoints to examine the nature of such interactions, producing a clearer picture of the interaction across the full range of both variables.

4.9. Summary

This study is the first to test a mediational model to test the hypothesis that PWV is a mediator of the relationship between diabetes and cognitive performance. The results indicated that PWV mediated the association between diabetes and cognitive performance. This mediational relationship was modified such that the indirect effect of diabetes through PWV was positive for younger individuals, and negative for older individuals. Additionally, associations were magnified in *APOE*-ε4 carriers. It is important to note that PWV did not fully mediate the diabetes-cognitive performance relationship and that the indirect relationship between diabetes and cognitive function was small compared with the direct relationship between diabetes and cognitive function. Further study of other mediators is important.

4.10. Implications for Clinical Practice

The data have important implications with regard to populations of individuals because of the prevalence of diabetes at all ages and the increasing prevalence of adult onset diabetes with advancing age. Clinical trials will be necessary to determine the reduction in cognitive decrement or impairment in relation to treatment for diabetes. However, our data indicate that PWV plays a role in the relation between diabetes and

cognition and that information on *APOE* genotype may be very important in the neuropsychological diagnostic context.

Although no treatments for *APOE* genotype are available at present, several treatment targets have been suggested for consideration in future studies. These include pharmacological methods of converting apoE-ε4 to a molecule resembling apoE-ε3, increasing apoE levels, and increasing apoE receptor expression (Bu, 2009). It will be interesting to see in future clinical trials if these therapies will alleviate the cognitive impairment seen in diabetic *APOE*-ε4 carriers.

At this time there are ethical considerations with respect to routinely assessing *APOE* genotype as part of routine diagnostic examination and with respect to use of these data once obtained (Roses, 1997). Whether *APOE*-ε4 genotype should be routinely obtained on patients, even diabetic patients, is controversial given the social and employment implications of revealing this information. Data on the importance of *APOE*-ε4 to the diagnosis and treatment of dementia may play an important role in the final resolution of this issue.

While the reporting of and *APOE* × diabetes interactions are important in terms of population risk for lowered cognitive performance, the major finding of this study was that PWV partially mediates between diabetes and cognitive performance. Higher levels of PWV can be lowered by the same sets of drugs that lower hypertension and prevented by the same set of lifestyle alterations that prevent hypertension.

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