APPROVAL SHEET

Title of Thesis: Relations of Pulse Wave Velocity and Sociodemographic Variables to Cognitive Functioning in Urban Dwelling African American and White Adults.

Name of Candidate: Peter Hansen MacIver
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Thesis and Abstract Approved: Shari Waldstein

Shari Waldstein, Ph.D.
Professor
Department of Psychology

Date Approved: 11/29/20

ABSTRACT

Title of Document:	RELATIONS OF PULSE WAVE VELOCITY AND SOCIODEMOGRAPHIC VARIABLES TO COGNITIVE FUNCTIONING IN URBAN DWELLING AFRICAN AMERICAN AND WHITE ADULTS.
	Peter H. MacIver, M.A., 2020.
Directed By:	Professor Shari Waldstein, Department of Psychology.

Arterial stiffness, or the physical hardening of the central large arteries, is a prevalent type of subclinical vascular disease that is predictive of incident systolic hypertension, coronary heart disease, stroke, and heart failure, all of which are leading causes of mortality in the developed world. Greater pulse wave velocity (PWV) is an indicator of greater arterial stiffness as the elastic properties of the arterial walls deteriorate. Prior cross-sectional and longitudinal investigations have demonstrated significant relations of greater PWV with lower levels of cognitive function and increased cognitive decline. However, to our knowledge, there are no prior studies examining relations of PWV to cognitive function using a comprehensive neuropsychological battery within a diverse sample of urban-dwelling adults that includes traditionally vulnerable and disenfranchised persons. Furthermore, much of the research linking PWV and cognitive function includes adjustments for basic demographic variables such as race and socioeconomic status but does not examine these variables as potential effect modifiers. The purpose of the present study sought to compute and examine the relations of PWV, race, and poverty status on various cognitive outcomes, and to examine whether these associations

withstood adjustments for cardio-metabolic risk factors and depression symptomatology. Analysis revealed a significant PWV, race, and poverty status interaction on the Brief Test of Attention (BTA) such that amongst whites living in poverty, higher BTA scores were observed in the presence of higher PWV. Furthermore, there were two significant PWV and poverty status interactions on the cognitive domains of California Verbal Learning Test (CVLT) delayed Recall and Verbal Fluency. In these interactions, higher cognitive outcomes were seen in those living in poverty in the presence of higher PWV. These results are in direct conflict with much of the previous literature. This was the first study, to our knowledge, that examined the interactive associations of PWV, race, and poverty status on a comprehensive neuropsychological battery and examined these interactions within a biopsychosocial framework. In light of these findings, it is possible that those living in poverty are able to utilize particular resilience strategies that enable quick and efficient adaptive set shifting in order to survive in unpredictable environments. Furthermore, these results raise the possibility of non-linear associations of PWV and cognition given the mean age and overall range of PWV observed in the sample.

RELATIONS OF PULSE WAVE VELOCITY AND SOCIODEMOGRAPHIC VARIABLES TO COGNITIVE FUNCTIONING IN URBAN DWELLING AFRICAN AMERICAN AND WHITE ADULTS.

By

Peter H. MacIver.

Thesis submitted to the Faculty of the Graduate School of the
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Dedication

The following thesis is dedicated to my wonderful and loving parents. Without their support, none of this would be possible. I am so very thankful for your love and support. I would also like to thank my friends at UMBC, as well as my committee members.

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Abbreviation Table

Abbreviation	Full Term
AA	African American
AI	Augmented Index
AIDS	Acquired Immunodeficiency Syndrome
APOE	Apolipoprotein E
A1C	Glycated hemoglobin
BMI	Body Mass Index
BTA	Brief Test of Attention
BVRT	Benton Visual Retention Test
CES-D	Center for Epidemiological Study Depression
cfPWV	Carotid to femoral Pulse Wave Velocity
CVD	Cardiovascular Disease
CVLT	California Verbal Learning Test
DSB	Digit Span Backward
DSF	Digit Span Forward
ECG	Electrocardiogram
HANDLS	Healthy Aging in Neighborhoods of Diversity Across the Lifespan
HR	Heart Rate
HVLT	Hopkins Verbal Learning Test
LLCI	Lower Limit Confidence Interval
LOPES	Louisville Older Persons Events Schedule
LVH	Left Ventricular Hypertrophy
MAP	Mean Arterial Pressure
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MR	Mineralocorticoid Receptor
m/s	Meters per second
NIA	National Institute on Aging
PP	Pulse Pressure
PWV	Pulse Wave Velocity
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SECPT	Socially Evaluated Cold Pressor Test
SES	Socioeconomic Status
SPSS	Statistical Package for the Social Sciences
3MS	Modified Mini Mental State
TMT	Trail Making Test
TMTA	Trail Making Test Part A
TMTB	Trail Making Test Part B
ULCI	Upper Limit Confidence Interval

VCI	Vascular Cognitive Impairment
VF	Verbal Fluency
WAIS-R	Wechsler Adult Intelligence Scale-Revised

Introduction

Decline in select domains of cognitive function (such as conceptual reasoning, processing speed, and memory) is often considered an inherent part of brain aging (Harada, Natelson Love, & Triebel, 2013). For some, such decline may portend emergence of cognitive impairment and dementia (Gorelick et al., 2011). However, a debate exists within cognitive aging research as to whether cognitive decline is attributable solely to inherent maturational processes (i.e., primary aging), versus age-related disease and environmental context (i.e., secondary aging; Anstey, Stankov, & Lord, 1994). Cardiovascular disease (CVD) and its risk factors are considered critical dimensions of secondary aging and have been widely established to have negative impact on cognitive functioning and trajectories of cognitive decline (Dregan, Stewart, & Gulliford, 2013; Jefferson et al., 2015; Leritz, McGlinchey, Kellison, Rudolph, & Milberg, 2011). Furthermore, CVD and its risk factors have been well established as risk factors for mild cognitive impairment (MCI; a cognitive decline greater than normal for an individual's age but not affecting daily living), and both Alzheimer's disease and vascular dementia, wherein cognitive impairments cause difficulties in everyday functioning (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Kivipelto, Laakso, Tuomilehto, Nissinen, & Soininen, 2002; Ott et al., 1998; Waldstein & Elias, 2015).

Subclinical vascular disease is an intermediate stage of cardiovascular pathophysiology that is linked to vascular risk factors and precedes clinical CVD (Waldstein & Elias, 2015). It is highly predictive of incident CVD (O'Donnell & Elosua, 2008) and has been associated with worsened trajectories of cognitive decline, and cross-sectional decrements in memory, attention, and executive functioning (Leritz et al., 2011; Yaffe, Kerr, Damera, Sarma, Inati, & Zaghloul 2014). Thus, it is paramount to develop a better understanding of the ways in which subclinical

vascular disease contributes to premature cognitive decline to promote successful cognitive aging and improve preventative interventions for MCI and dementia.

Arterial stiffness, or the physical hardening of the central large arteries, is a prevalent type of subclinical vascular disease (Cecelja & Chowienczyk, 2012) that is predictive of incident systolic hypertension, coronary heart disease, stroke, and heart failure, all of which are leading causes of mortality in the developed world (Shirwany & Zou, 2010). Central arterial stiffness increases with age and has been shown to aggravate harmful vascular phenotypes in diabetes, atherosclerosis, and renal disease (Shirwany & Zou, 2010; Zieman, Melenocsky, & Kass, 2005). There exist a variety of techniques to measure the stiffness of the aorta and surrounding central arteries, with pulse pressure (PP) (i.e., systolic blood pressure minus diastolic blood pressure) and pulse wave velocity (PWV) being most commonly used. Greater PWV is an indicator of greater arterial stiffness as the elastic properties of the arterial walls deteriorate (Al Hazzouri et al., 2013) and is considered the "gold standard" measure of arterial stiffness due to its low sensitivity to cardiac function, which has a greater impact on PP (Mitchell, 2009).

Prior cross-sectional and longitudinal investigations have demonstrated significant relations of greater PWV with lower levels of cognitive function and increased cognitive decline. In that regard, Fujiwara et al. (2005) determined that higher PWV was associated with poor global cognitive functioning within a community sample of Japanese elders in one of the first cross-sectional studies to demonstrate an association of elevated arterial stiffness with cognitive function in a non-demented population. Specifically, the highest tertile of PWV (>2070 cm/sec) was associated with worse cognitive outcomes on the Mini-Mental State Examination (MMSE), a brief cognitive screening measure. This result was later replicated in a meta-analysis pooled study of both cross-sectional and longitudinal studies (Pase, Herbert, Grima, Pipingas, &

O'Rourke, 2011) that found associations of greater carotid-femoral PWV (cfPWV) with lower scores and/or greater decline on the MMSE. Greater PWV has also been associated with decline in cognitive performance on more extensive neuropsychological batteries (Waldstein, Carrington, Thayer, Najjar, Scuteri, & Zonderman, 2008; Pase et al., 2016). However, to my knowledge, there are no prior studies examining relations of PWV to cognitive function using a comprehensive neuropsychological battery within a diverse sample of urban-dwelling adults that includes traditionally vulnerable and disenfranchised persons. Furthermore, much of the research linking PWV and cognitive function includes adjustments for basic demographic variables such as race and socioeconomic status but does not examine these variables as potential effect modifiers. Failure to examine racial and socioeconomic moderators of PWV-cognition relations negates the opportunity to identify whether individuals of disenfranchised backgrounds (e.g., African Americans living in poverty) exhibit greater vulnerability to the negative impact of PWV on cognitive function. Additionally, the majority of the literature utilizes simultaneous entry of covariates in examining PWV-cognition relations, several of which may operate, at least in part, as mediators of these associations rather than confounders. We therefore propose hierarchal entry of select biopsychosocial variables, including depressive symptomatology and cardiometabolic risk factors and comorbidities, to examine whether relations of PWV and cognitive function withstand these adjustments.

The purpose of the present study is twofold: (1) to examine the interactive relations of PWV, race, and poverty status on cognitive performance within a sample of African-American and White urban-dwelling adults and (2) to determine whether these associations withstand hierarchal adjustments for select CVD risk factors (e.g., depressive symptoms, cardiometabolic risk factors). The neuropsychological battery assesses multiple domains of function, including

attention, working memory, verbal learning, verbal memory, nonverbal memory, verbal fluency, perceptuo-motor speed, and executive functioning.

This thesis begins with a literature review outlining cognitive aging, and the role of clinical and subclinical vascular disease in this process. This will be followed by a review of the literature analyzing the relation between arterial stiffness and cognitive function. Next, race and SES will be discussed as potential moderators in the relation of PWV to cognitive function. This will be followed by a discussion of the potential underlying distal and proximal mechanisms linking PWV and cognition, including correlated biopsychosocial risk factors. Then, the study aims, hypotheses, methodology, and data analytic procedures will be discussed. The results from the data analysis will then be reported. Subsequent discussion on each of the studies models will be presented and will include proposed cognitive and biological mechanism of these interactions. Finally, the study's strengths and limitations, as well as implications and recommendations for future work will be outlined before the paper's conclusion.

Literature Review

Cognitive Aging

With increased age, performance in select domains of cognitive function decline to varying degrees. While decrements may arise in cognitive domains such as conceptual reasoning, memory, processing speed, and attention, other domains such as vocabulary and crystalized intelligence may actually improve into late life (Harada et al., 2013). The trajectories of these declines in older adults are extremely heterogeneous and vulnerable to a multitude of variables that may act as protective and/or vulnerability factors. The shape of these trajectories also varies and does not always manifest as linear patterns of decline (Smits et al., 2014). Further research is

needed to elucidate the ways in which systemic disease states and environmental influences modify age-related cognitive trajectories.

As disease becomes more prevalent with increased age, the ability to fully understand the "normal" aging process becomes confounded. This raises the question of whether an organism's deterioration results from acquiring harmful diseases, or whether the deterioration simply emanates from the intrinsic maturation of an organism's physiology. This question is summarized by the dual-process nature of aging that posits primary aging as the maturational processes that renders an organism susceptible to disease and secondary aging as the development of disease that subsequently causes aging (Anstey, Stankov, & Lord, 1994). Early concepts of this dual-process on cognitive function proposed that primary aging was related to decline in perceptual speed, whereas secondary aging contributed to decline in perceptual speed, perceptual reasoning, verbal comprehension, and reasoning abilities (Anstey, Stankov, & Lord, 1994). Investigators then theorized a much broader impact of systemic health and disease (as indicators of secondary aging) on cognitive decline (Waldstein, 2000). An argument remains within aging research as to the exact nature of the cognitive aging process, with more work needed to clarify the association of primary and secondary aging with trajectories of cognitive decline.

Cardiovascular Disease and Cognitive Aging

Cardiovascular disease is an umbrella term referring to diseases of the heart, vascular diseases of the brain, and diseases of the blood vessels (Mendis, Puska, & Norrving, 2011). The underlying etiologies of these diseases are diverse and are influenced by multi-level risk factors such as atherosclerosis, high blood pressure, smoking, alcohol, diabetes, activity level, psychosocial status, and environment (Sing, Stengard, & Kardia, 2003; Thayer, Yamamoto, &

Brosschot, 2010; Waldstein & Elias, 2015). Many of these risk factors have been shown to influence cognitive function. In that regard, a substantial literature demonstrates robust relations of a broad range of cardiovascular risk factors and diseases on lower levels of cognitive function and cognitive decline across the life span, in addition to increased risk of cognitive impairment and dementia (see Waldstein & Elias, 2015).

The term vascular cognitive impairment (VCI) has been increasingly used to describe the spectrum of cognitive impairment associated with stroke, vascular brain injury, or subclinical disease. The most severe end of this spectrum is commonly referred to as vascular dementia. It is now well recognized that an interplay between vascular and Alzheimer's disease pathologies are associated with heterogeneous cognitive trajectories in aging (Gorelick et al., 2011). However, cardiovascular risk factors and diseases exert a negative impact on cognitive performance and cognitive aging long before dementia or stroke manifest (Waldstein & Elias, 2015).

Subclinical Vascular Disease and Cognitive Aging

The presence of subclinical vascular disease increases the risk of clinical manifestations of CVD, including acute events (Enserro, Vasan, & Xanthakis, 2018), and is associated with an accelerated aging process. In a longitudinal assessment of successful aging, participants with a baseline history of subclinical vascular disease were similar in age-related health decline to individuals five years older without subclinical vascular disease (Newman et al., 2003). Additionally, a cross-sectional study of 400 healthy men found an association between markers of subclinical vascular disease, including greater intima-medial thickness, PWV, and ankle-brachial blood pressure index, and lower scores on tests of processing capacity and executive functioning (Muller, Grobbee, Aleman, Bots, & van der Schouw, 2007). These subclinical

vascular disease markers have similarly been associated with poorer cognitive function and cognitive impairment (Benetos et al., 2012).

Because subclinical vascular disease offers strong predictive utility with respect to the development of clinical disease states, its markers are commonly targeted for prevention and early intervention efforts. Further, the quick and noninvasive way in which many forms of subclinical vascular disease can be measured makes the study of these variables relatively easy. However, the relations of subclinical vascular disease to cognitive function and decline is likely to be multifactorial and complex (Jefferson et al., 2015). PWV is considered a critically important manifestation of subclinical vascular disease that influences cognitive performance and cognitive aging trajectories (Wendell & Waldstein, 2015).

Defining PWV and Understanding its Utility

PWV is a direct assessment of stiffness in the aortic tree and is an indicator of subclinical vascular disease (Al Hazzouri et al., 2013). Arterial compliance represents the ability of the arterial system to accommodate the systolic ejection volume. Arterial stiffness represents the dynamic force, called impedance, opposing this ejection, with low stiffness representing greater efficiency of the arterial system to accommodate ejection. PWV is measured by dividing the physical distance between two standard measurement sites by the difference in time it takes for an aortic pulse wave to reach two measurement points (Al Hazzouri et al., 2013). Standard guidelines for PWV measurement typically have an individual rest in a supine position for at least 5-10 minutes to reach physiological baseline before the assessment. Measurement of PWV is usually followed within minutes with an assessment of brachial artery blood pressure to facilitate interpretation of PWV, as it partly depends on systolic pressure within the arterial tree

(Boutouyrie et al., 2009). Researchers have derived several formulas for computing PWV. During the end of the 19th century, the method to calculate PWV was determined by formula 1.1:

$$PWV^2 = Eh / 2r\rho \quad (1.1)$$

E is the measurement of elastic modulus of the arterial wall, h is arterial thickness, r is arterial radius, and ρ is blood density (Boutouyrie et al., 2009). This formula was modified in the early 20th century to instead include the relative change in volume ($\Delta V / V$) and pressure (ΔP) seen in formula 1.2 (Bramwell & Hill, 1922; Boutouyrie et al., 2009):

$$PWV^2 = (\Delta PV) / (\Delta V\rho) \quad (1.2)$$

Both of these formulas demonstrate PWV as a direct measurement of arterial stiffness as it is the square value of 1/distensibility, or dilation ability of the arteries.

There is currently no consensus regarding the threshold at which PWV becomes dangerous. Nilsson, Khalili, and Franklin (2014) specify a carotid-femoral PWV of greater than 10 meters per second (m/s) as the threshold for increased risk of tissue damage, while Scuteri and Wang (2014) cite 12 m/s. Carotid to femoral PWV is the most widely used index of arterial stiffness and has demonstrated strong predictive value with respect to incident CVD (Boutouyrie et al., 2009; de Simone et al., 1999). Other measurement sites include carotid-radial, branchial-radial, branchial-ankle, and femoral-tibial. PWV is the "gold standard" measure of arterial stiffness due to its low sensitivity to cardiac function. But other indices, including pulse pressure (PP; difference between systolic and diastolic blood pressure) and augmented index (AI; measure

of stiffness derived from the ascending aorta pressure waveform) are commonly used as indirect markers of arterial stiffness (Mitchell, 2009).

With increasing age, the arteries throughout the body become stiffer. This vessel hardening is believed to begin in the aorta and slowly progress to the vasculature in other organs, including the brain. Muscular arteries, by contrast, do not undergo stiffening with age (Najjar, Scuteri, & Lakatta, 2005). With this increased arterial stiffness, the pressure and amplitude of the reflected wave off the arteries increases and damages downstream vessels (Gauthier et al., 2015; O'Rourke & Hashimoto, 2007). Additionally, the thickness of the arterial wall (indexed by the intimal and medial layers) triples between the ages of 20 and 90 years (Najjar, Scuteri, & Lakatta, 2005). The physiological cause of stiffness is believed to be two-fold. Accumulation of advance glycation end-products in arterial smooth muscle cells alters their physical properties and causes stiffness of the fibers. Second, calcium deposits increase in the arterial wall, especially after the fifth decade (Lee & Oh, 2010) as a result of persistent cyclic stress on the elastin, causing fatigue and fracturing of the elastin proteins (Nilsson, Khalili, & Franklin, 2014). Stiffness also partially depends on distending pressure and vascular smooth muscle tone (McEniery et al., 2006). With increased stiffness, the pulse wave reflection arrives back to the aorta earlier during systole. As a consequence, the systolic blood pressure is augmented and the diastolic blood pressure becomes reduced, increasing the pulse pressure (Pase et al., 2011). The increased systolic blood pressure associated with arterial stiffening subsequently increases hemodynamic pulsatility, which is a predictor of stroke (Lee et al., 2014; Mattace-Raso et al., 2006). PWV is also an independent predictor of atherosclerosis, death from CVD, and all-cause mortality (Fujiwara et al., 2005; Laurent et al. 2001; Meaume, Benetos, Henry, Rudnichi, & Safar, 2001; Mitchell et al., 2010).

Demonstrated Link Between Arterial Stiffness and Cognitive Function

Multiple studies have demonstrated that elevated PWV is associated with lower scores on the MMSE, a brief (5-10 minute) screening measure of global cognitive status (Tombaugh, McDowell, Kristjansson, & Hubley, 1996). The MMSE has demonstrated moderate to high reliability, high sensitivity for detecting cognitive impairment in patients suffering from moderate to severe Alzheimer's disease, and accurately reflects cognitive decline in dementia patients (Tombaugh et al., 1996). Because the MMSE is quick to administer, it is often a preferred assessment in epidemiological and clinical studies of cognitive decline (Aggarwal & Kean, 2010). However, the MMSE has also been criticized for its lack of discrimination between those with mild dementia and non-demented persons, limited ability to detect impairment from focal lesions, and a large number of false-positive errors among those with low levels of education (Tombaugh et al., 1996). Furthermore, due to its brevity and its main use as a global cognitive screening measure, the MMSE is minimally informative in determining difficulties in specific cognitive domains as compared to a more extensive neuropsychological battery.

Much of the research to date has utilized the MMSE in demonstrating PWV's association with cognitive function. Scuteri, Brancati, Gianni, Assisi, & Volpe (2005) found that PWV was inversely associated with performance on the MMSE in a cross-sectional study of patients free of dementia, stroke, and arterial fibrillation. These associations withstood adjustments for age, gender, cardiovascular risk factors, and cardiovascular disease. P. M. Nilsson et al. (2014) similarly demonstrated that a PWV greater than 13.8 m/s was associated with impaired performance on the MMSE after adjustment for demographic and cardiovascular risk factors. Scuteri et al. (2007) found that PWV was the single strongest independent predictor of decline on the MMSE in a longitudinal assessment of Italian elders (median follow up of 12 months).

Specifically, they found that for every 1 m/s increase in PWV, MMSE scores declined by 0.74 points per year (Scuteri et al., 2007). Similar findings have been noted in larger samples of elderly participants (Benetos et al., 2012). A longitudinal investigation conducted in the United States demonstrated that MMSE scores decreased by 0.30 points per year in a low PWV group and decreased by 0.45 points in a high PWV group. Furthermore, those in the high PWV had substantially greater odds of displaying greater than a 5-point decrease in MMSE score at a nine year follow up compared to their low PWV counterparts (Al Hazzouri et al., 2013). Recent work has demonstrated that elevated brachial-ankle PWV is also an independent predictor of global cognitive decline in a community sample of older adults (Taniguchi et al., 2015). In aggregate, the research to date strongly suggests that PWV has a negative impact on MMSE performance. But due to the MMSE's brevity, the generalizability of PWV's relation to performance in specific domains of cognitive function is not ensured.

Fewer available studies have implicated elevated PWV in lower levels of cognitive function and/or cognitive decline on a broad range of neuropsychological tests. Cross-sectional associations of aortic stiffness with cognitive functioning were examined in the Framingham Heart Study Third Generation cohort where PWV was measured in the carotid and femoral arteries (Pase et al., 2016). Results indicated that greater aortic stiffness was associated with worse performance on Trails B, the difference between Trails B and A, and the Visual Reproductions delayed recall test, which reflect the cognitive domains of processing speed, executive function, and visual memory. Aortic stiffness remained a predictor of the Trails B minus A difference score in a fully adjusted model that controlled for biomedical indices and health behaviors; however, the other associations were rendered non-significant after adjustments (Pase et al., 2016). Data from the Maine-Syracuse Longitudinal study further

demonstrated associations between elevated PWV and poorer performance on tests of global cognitive function, visual spatial memory, scanning and tracking, and verbal episodic memory (Elias, Robbins, Budge, Abhayaratna, Dore, & Elias, 2009). Cross-sectional relations of greater cfPWV with poorer performance on multiple measures of executive functioning were also noted among a non-demented older Asian cohort in Singapore (Lim et al., 2016).

Elevated PWV has further been associated with prospective decline on the Benton Visual Retention Test (visual memory), California Verbal Learning Test (CVLT) free recall short delay, CVLT free recall long delay (verbal learning and memory), and the Blessed Information Memory Concentration Test (episodic memory; Waldstein et al., 2008). Similarly, Hajjar, Goldstein, Martin, & Quyymi (2016) found that higher PWV was associated with steeper declines on measures of executive functioning, memory, and working memory. This group's cohort was comprised of 24% ethnic minorities and 76% White persons, and the average amount of education obtained was almost 19 years (Hajjar et al., 2016). This reflects a strong trend in the above literature to use samples that are largely homogeneous and highly educated. Additional research is needed to confirm the existence of relations between PWV and cognitive function in heterogeneous samples using a comprehensive neuropsychological battery.

Corroborating studies of PWV and cognitive function, PP, another index of arterial stiffness, has also been associated with cognitive function and decline. PP rises noticeably in the fifth decade due to arterial stiffening (Chae, Pfeffer, Glynn, Mitcheel, Taylor, & Hennekens, 1999). Higher PP has been associated with impairments in global cognitive functioning and attention (Riba-Llena et al., 2016), greater decline on tests of verbal learning and a cognitive screening measure (Waldstein et al., 2008), episodic memory performance and retrieval speed (Pase et al., 2010), and memory function and language (Yaneva-Sirakova, Tarnovska-Kadreva,

& Traykov, 2012). Research has suggested a possible U-shaped association between PP and cognitive function, with both high and low PP predicting cognitive decline in patients with stroke or transient ischemic attack (Wang et al., 2015).

In contrast to the above investigations, a number of studies have failed to identify significant relations of PWV or PP to cognitive function or decline. In that regard, Pase et al. (2010) found no significant relations of PP to decline in working memory and attention. Further, results of studies in Sweden and Australia found an absence of relation of PWV with cognitive functioning in cognitively healthy elderly individuals (Gustavsson et al., 2015; Singer et al., 2013). Similarly, a study in Japan found no significant associations of brachial-arterial PWV and cognitive impairment in community-dwelling elderly individuals over 60 years of age (Sugawara et al., 2010). An analysis of data from the Rotterdam Study failed to find an association between baseline PWV and longitudinal decline in cognitive performance on the MMSE, Letter-Digit Substitution Task (executive function), and Word Fluency (executive function). However, after adjustment for cardiovascular risk factors, this group did note an association between elevated PWV and poorer performance on Trial 3 of the Stroop Color-Word Test, a measure of processing speed and inhibitory control (Poels et al., 2007). Lastly, Singer et al. (2013) found that elevated PWV was related to cognitive decline in global functioning and memory in men, but not in women.

While conflicting evidence exists, results generally suggest an association between elevated PWV and decreased performance on cognitive measures in both cross-sectional and longitudinal studies of non-demented persons. However, much of the research has utilized the MMSE, a brief screening measure of overall cognitive ability (Tombaugh & McIntyre, 1992). Overreliance on the MMSE limits an understanding of the relation of arterial stiffening to

performance in specific cognitive domains. Thus, studies that include more comprehensive neuropsychological batteries offer the ability to examine the specific cognitive domains affected by PWV. Although several investigations have indeed employed extensive neuropsychological batteries, demonstrating relations of greater PWV to lower levels of performance on tests of executive functioning (Elias et al., 2009; Lim et al., 2016), attention (Pase et al., 2016), visual searching (Pase et al., 2016; Elias et al., 2009), visual spatial memory (Elias et al., 2009), verbal memory (Elias et al., 2009; Waldstein et al., 2008), and episodic memory (Waldstein et al., 2008), these studies have used homogeneous samples of predominantly White and well educated individuals. To my knowledge, there is no previous work investigating the association between PWV and performance on a comprehensive neuropsychological battery within a biracial and socioeconomically-diverse cohort.

This thesis extends the prior literature by utilizing an extensive neuropsychological battery spanning multiple cognitive domains within a biracial urban-dwelling sample derived from the local epidemiological Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS) study. Furthermore, no prior research has simultaneously examined the potential moderating influences of race and SES on PWV-cognition relations. Inclusion of these moderators is crucial for elucidating potential vulnerability to the negative impact of PWV displayed by historically disenfranchised groups of individuals.

Rational for Race and SES as Potential Moderators

Race.

Race is not a biological variable but is instead a complex social construct that represents multiple influences including culture, ancestry, and common origin (Kittles & Weiss, 2003). Because of historical influences and the construction of institutional norms in the United States,

African Americans often experience hardships that are uniquely different from their White peers. By studying race, scientists are able to explore the mixture of unique experiences that contribute to health and cognitive outcomes. To my knowledge, no previous work has investigated the moderating role of race on the association between arterial stiffness and cognitive function.

African Americans have been found to have greater arterial stiffness (Al Hazzouri et al., 2013; Heffernan, Jae, & Fernall, 2007; Rosano et al., 2013), higher rates of hypertension (Kramer et al., 2004) and lower rates of blood pressure control than non-Hispanic Whites (Delgado, Jacobs, Lackland, Evans, & de Leon, 2012). This may be explained by multiple biopsychosocial risk factors such as impaired microvascular functioning (Morris et al., 2013) and greater psychosocial risk (Lewis et al., 2010). However, there has been conflicting evidence on racial differences in aortic stiffening. For example, the Multiethnic Study of Atherosclerosis failed to find an ethnic difference in arterial stiffness in participants aged 45 to 84 years (Duprez et al., 2009). Although findings are mixed, it is possible that elevated levels of PWV in African Americans may make this group particularly vulnerable to associated cognitive difficulties.

With respect to cognitive function, African Americans tend to demonstrate lower levels of performance on neuropsychological and cognitive screening tests compared to their White peers (Manly, Jacobs, Touradji, Small, & Stern, 2002; Morgan, Marsiske, & Whitfield 2008). These differences in cognitive function between racial groups become particularly pronounced later in life, with African Americans displaying earlier and more frequent diagnoses of cognitive impairment (Whitfield, 2002). African Americans elders are judged to be cognitively impaired on dementia batteries more frequently than Whites (Morgan, Marsiske, & Whitfield 2008). However, it is important to note that measurement biases may underestimate performance among African American in cognitive aging and lifespan studies (Glymour & Manly, 2008). In addition,

between-group differences in reading levels disproportionately and negatively impact African Americans' test performance (Morgan et al., 2010). Further, many of the neuropsychological tests currently employed today were normed using homogeneous White samples, creating a need for normative measures from minority groups (Casaletto et al., 2015).

African Americans are thought to be vulnerable to multi-level risk factors that confer negative effects on cognitive function. These range from distal environmental influences (i.e. neighborhood resources) to proximal variables (i.e. health behaviors, prevalent disease, and poor access to medical care). Hypersegregation (defined as extreme levels of residential segregation by race) has been suggested as a basis for socioeconomic constraint on African Americans in urban settings (Glymour & Manly, 2008; Massey & Denton, 1989). Neighborhood of residence influences proximity and quality of schools, grocery stores, job opportunities, and medical access, as well as environmental stressors (Kawachi & Berkman, 2003). Additionally, racial segregation contributes to school segregation and educational quality. Indeed, education is a strong predictor of cognitive function and impairment (Glymour & Manly, 2008). Systematic differences do exist between African Americans and Whites in quality of education, which then reinforce racial differences on cognitive test performance (Glymour & Manly, 2008). African American adults, on average, are likely to have attained less formal education than White adults (Kao & Thompson, 2003). The brain battering hypothesis posits that individuals with lower levels and lesser quality education are at greater risk for vascular damage and overall dementia risk (Del Ser et al., 1999). These distal influences can then coincide with proximal risk factors on cognitive function. Additionally, African Americans have higher rates of sedentarism and obesity, a greater prevalence of the APOE e4 allele, higher burden of diabetes, and higher rates of hypertension than Whites (Bolen et al., 2010; Kramer et al., 2004; Logue et al., 2011; Peek,

Cargill, & Huang, 2007; Williams & Jackson, 2005). These disproportionate exposures experienced by African Americans are likely to compound upon each other, rendering this group particularly vulnerable to negative influences of PWV on cognitive functioning.

Socioeconomic Status.

SES is a complex construct that is often measured by educational level, income, occupation, or some similar combination (Rawshani, Svensson, Rosengren, Eliasson, & Gudbjornsdotttir, 2015). No variable fully encompasses the complexities of social advantage and disadvantage. The multiple pathways influencing the connection between SES and CVD include, but are not limited to, effects of chronic stress, differences in lifestyle and behavior, greater prevalence of cardiometabolic risk factors and diseases, and less access to healthcare (Pickering, 1999). High school education, low levels of income, and lower neighborhood SES were associated with higher PWV in a cross-sectional investigation of racial and socioeconomic disparities in arterial stiffness (Thurston & Matthews, 2009). Lower levels of SES have further been associated with more rapid aortic stiffening (Trudel, Shipley, McEniery, Wilkinson, & Brunner, 2016). In that regard, using data from the Whitehall II study in Great Britain, Trudel et al. (2016) found that lower educational attainment was associated with more rapid progression of aortic stiffening after adjustment for demographic and other cardiovascular indicators. Interestingly, interactions of SES and race have revealed that higher SES African Americans have greater PWV than lower SES African Americans, lower SES Whites, and higher SES Whites, suggesting a particular vulnerability to subclinical vascular disease (Wendell, Waldstein, Evans, & Zonderman, 2017). This finding is consistent with the hypothesis of diminished returns which states that as SES increases, Black adults do not experience the same health improvements as White adults (Farmer & Ferraro, 2005).

Higher levels of educational attainment have been linked to better vascular and cognitive outcomes, as well as larger brain gray and white matter volumes (Mortby et al., 2014). It has been suggested that these differing volumetric outcomes may, in part, mediate the association between education and cognitive function (Mortby et al., 2014). The "cognitive reserve" hypothesis stems from animal studies in which different life experiences were shown to affect brain structure, including vasculature, brain cells, and synapses. The addition of this neural matter as a result of enriched life environment is hypothesized to buffer against neuropathological effects by providing functional compensation and more efficient neural networks (Mortby et al., 2014). In humans, cognitive reserve similarly represents structural and functional brain advantage that results from higher educational levels and other measures of socioeconomic advantage and leads to higher cognitive test scores and better preservation of functioning after injury. Thus, cognitive reserve is thought to reflect brain reserve capacity (Lezak, Howieson, Bigler, Tranel, 2012).

Multiple indices of socioeconomic status such as education, income, and occupation may be seen as markers of cognitive reserve that protect against cognitive decline and dementia (Singh-Manoux & Kivimaki, 2010; Stern, 2009). Viewed within this framework, individuals with higher socioeconomic status may be better able to physiologically adapt to consequences of arterial stiffening, avoid adverse cognitive sequalae, and demonstrate higher levels of cognitive functioning. Furthermore, like African American ethnicity, those of low socioeconomic status are likely to experience a multitude of risk factors (e.g., financial burden, poorer health and health care quality, poorer neighborhood resources) that may render this group more vulnerable to the negative impact of PWV on cognition.

Multiple indicators of SES (e.g., education, income, occupation, neighborhood) may moderate the relations of PWV to cognitive function. Poverty status will be used as an indicator of socioeconomic status in this investigation as it was the primary measure of SES used for selection (and group stratification) in the Healthy Aging in Neighborhoods of Diversity across the Lifespan (HANDLS) study, which will provide the data for the analyses (Evans et al., 2010). Poverty status was calculated based on household size and reported family income relative to 125% of the 2004 Federal poverty threshold ($18,850 for a family of 4). While education and occupation measure individual dimensions of SES, household income is a better reflection of the standard of living and of life experience of household members by shared goods and services (Duncan, Daly, McDonough, & Williams, 2002). Family income has been the most widely used indicator in studies of SES and health in the United States (Duncan et al., 2002). Additionally, economic measures have been found to be more sensitive in SES-mortality associations as compared to measures of education or occupation (Duncan et al., 2002). Education will be used as an adjustment variable in the present study as higher levels of education increase cognitive reserve and protect against cognitive decline (Mortby et al., 2014). To my knowledge, no prior studies have examined the moderating role of socioeconomic status on the relation between arterial stiffness and cognition.

Possible Mechanisms and Mediators of PWV-Cognition Associations

The primary hypothesis as to how arterial stiffness promotes cognitive decline is that augmented pressure pulses caused by aortic stiffness penetrate and damage small cerebral vessels that are not protected against pulsatile blood flow (de la Torre, 2012). The aorta, the artery immediately downstream of the heart's blood ejection, maintains a reservoir of pulsatile energy delivered by the left ventricular ejection at systole and discharges this energy during diastole.

The Windkessel effect refers to the protective mechanism that the aorta provides for the distal vasculature: its more compliant structure absorbs the kinetic energy of the waveform from left ventricular ejection and dampens excessive transmission of pulsatile flow that can damage smaller vessels (de la Torre, 2012; Hanon et al., 2005). The most proximal aorta reduces the wave reflection between the aorta and carotid artery, referred to as impedance mismatch, that reduces excessive kinetic energy transmission to the cerebral capillaries (de la Torre, 2012).

With arterial stiffening, the aorta losses elastin that leads to diminished compliant functioning. This causes an increase in PP and systolic blood pressure, increased PWV, and reduced wave reflections at the carotid arteries. These may be further exacerbated in the presence of vascular risk factors. As a result, exaggerated PWV is transmitted to microvessels in the brain. This increase in pulsatile flow has been associated with greater white matter disease and damage to endothelial cells that control cerebral blood flow (Mitchell et al., 2004). Thus, these physiological manifestations of reductions to the Windkessel effect may be linked to subsequent cognitive declines associated with arterial stiffening.

Specific distal brain regions at risk for white matter disease from increased arterial stiffness have been hypothesized. For example, it is suggested that the superior longitudinal fasciculus, which contains the parietal portion bundle (important for processing speed) and the temporal portion bundle (important for memory) may be particularly vulnerable to pulsatile blood flow as it travels across the fronto-parietal watershed regions. These watershed regions are perfused by arterioles with few interconnections available to preserve blood supply in the event of ischemic injury (Rosano et al., 2013). This may, in part, explain why subclinical and clinical CVD disproportionally impacts the cognitive domains of sustained attention, processing speed, executive functioning, and memory retrieval (Gorelick et al., 2011, Waldstein & Elias, 2015).

Microvascular damage to cerebral capillaries further leads to reduced cerebral blood flow. Brain ischemia has been associated with the accumulation of amyloid precursor proteins, beta-amyloid, expression of presenilin genes, and formation of free oxygen radicals within cerebral tissue. Subclinical vascular disease may further damage the blood-brain barrier, which may manifest in progressive neurovascular and neurodegenerative disease (Fujiwara et al., 2005; Johansson, 1994; Skoog et al., 1996).

A second hypothesis is that the relation of arterial stiffness to cognitive decline is largely or fully attributable to the presence of correlated CVD risk factors. Cardiovascular risk factors have well known negative impact on both PWV and cognitive functioning (Cecelja & Chowieczyk, 2009; Leritz et al., 2011; Mattace-Raso et al., 2010; Taquet et al., 1993). Further, greater PWV has been shown to promote increases in cardiovascular risk factors such as hypertension and atherosclerosis (Cecelja & Chowieczyk, 2009; Shirwany & Zou, 2010). Prior studies of the relations of PWV to cognitive outcomes have frequently adjusted for select CVD risk factors, and several studies have found that significant associations withstand such adjustments (Al Hazzouri et al., 2013; Elias et al., 2009; Fujiwara et al., 2005; Waldstein et al., 2008). However, one prior study found that most PWV-cognitive relations were rendered non-significant by adjustment for CVD risk factors (Pase et al., 2016). It is also unclear whether measures of CVD risk may have served as explanatory factors in prior studies of PWV and cognitive function that yielded null findings because all variables were entered simultaneously. To further examine this issue, we propose hierarchal entry of select CVD risk factors in order to explore whether significant PWV-cognition associations withstand sequential adjustments. Specifically, we will examine whether depressive symptomatology and correlated CVD risk factors and diseases negate any significant PWV-cognition associations. We posit that PWV-

cognitive function relations will be independent of these risk factors, therefore further suggesting pulsatility as a more likely mechanistic pathway. However, these variables will be explored as candidate mediators if they render any relations of PWV to cognitive function non-significant.

Depression.

Higher depressive symptomatology has been associated with greater arterial stiffness in large population-based studies (Seldenrijk et al., 2011). The vascular depression hypothesis has been theorized to explain the connection between depressive symptoms and vascular disease. Specifically, CVD may predispose, precipitate, and perpetuate depressive syndromes, especially among geriatric populations and those with atherosclerotic disease (Alexopoulos, Meyers, Young, Campbell, Silbersweig, & Charlson, 1997). Depression has a known negative impact on cognitive function; meta-analyses have found deficits in processing speed, attention, executive function, and attention among depressed individuals (Hasselbalch et al., 2011). In addition, imaging studies often find greater white matter disease burden, particularly in the frontal lobes and basal ganglia among those with depression (Heiden et al., 2005). Depressive symptoms, as measured by the Center for Epidemiological Study Depression scale (CES-D), will be examined in hierarchal analyses.

Cardiometabolic Risk Factors and Comorbidities.

Body mass index (BMI), diabetes, total cholesterol, and CVD comorbidities have been identified as potential mediators in PWV-cognition associations. Obesity (as classified as a BMI > 95th percentile for age) is associated with increased PWV compared to healthy controls (Çelik et al., 2011). Similarly, patients with type 2 diabetes have increased central artery stiffness as demonstrated by increased PWV, while total cholesterol is positively correlated with PWV (Im, Lee, Shim, Lee, & Lee, 2007; Zhang et al., 2011). Amar et al. (2001) demonstrated that the total

number of cardiovascular risk factors and presence of CVD was positively correlated with PWV. Furthermore, the presence, clustering, and worsening of CVD risk factors are associated with increased PWV over time in patients with type I diabetes (Dabelea et al., 2013).

The above risk factors have been associated with cognitive function as well. In this regard, elevated BMI has been associated with lower levels of cognition, particularly executive function. Specifically, cognitive switching has been shown to be worse in obese individuals compared to controls, indicating cognitive inflexibility (Steenbergen, & Colzato, 2017). Type 1 diabetes is most commonly accompanied by deficits in the cognitive domains of processing speed, psychomotor efficiency, motor speed, and executive functioning (Kodi & Seaquist, 2008). Likewise, patients with type 2 diabetes are likely to experience impairment in psychomotor speed, verbal memory, processing speed, verbal fluency, and visual retention (Kodi & Seaquist, 2008). Increased total cholesterol has been implicated in greater cognitive decline in longitudinal measurements (Ma, Yin, Zhu, Luo, Shi, & Gao, 2017). Comorbid CVDs are further likely to exacerbate the rate of cognitive decline. In that regard, coronary heart disease has been shown to accelerate cognitive decline in Alzheimer's disease by 66% compared to controls (Bleckwenn et al., 2017). These cardiometabolic risk factors all have the potential of imparting damage to neuronal tissue. Brain atrophy, lesion formation in grey and white matter, as well as cortical thinning are frequent consequences of these pathologies, arising from small vessel disease and other changes to the cerebral vasculature (Biessels & Reijmer, 2014; Waldstein & Wendell, 2010). BMI, diabetes, total cholesterol, and CVD co-morbidities will be entered together in hierarchical analyses.

Adjustment for Potential Confounders.

The proposed analyses will also include several adjustments for potential confounding variables with known association with PWV (and its assessment) and/or cognitive function. In that regard, all models will include covariates of age, education, sex, mean arterial pressure (MAP), heart rate (HR), cigarette smoking, alcohol use, and antihypertensive medication. These covariates are widely cited as potential confounders in the arterial stiffness and cognition literature (Al Hazzouri et al., 2013; Elias, Robbins, Budge, Abhayaratna, Dore, & Elias, 2009; Fujiwara et al., 2005; Gauthier et al., 2015; Lee et al. 2014, Pase et al., 2016; Waldstein et al., 2017) and were utilized in an earlier investigation of PWV and cognitive function from our group (Waldstein et al., 2008).

It is well established that arterial stiffness increases with age (Amar, Ruidavets, Chamotin, Drouet, & Ferrieres, 2001; Vaitkevicius et al., 1993). This is believed to result from accumulation of calcification in the intima media layer of arterial walls and endothelial dysfunction from continuous elastic stress with age (Lee & Oh, 2010). The most common cognitive domains negatively affected with increasing age are processing speed, working memory, and executive functioning (Murman, 2015).

Educational attainment is also associated with PWV and with cognitive function. Lower levels of education were associated with higher PWV in a cohort of American youths (Thurston & Matthews, 2009). Less educated men in Japan were found to have elevated brachial-ankle PWV (Saijo, Yoskioko, Fukui, Kawaharda, & Kishi, 2008). Not surprisingly, higher levels of education are associated with better performance on cognitive tests (Byrd, Sanchez, & Manly, 2005). Additionally, more years of education have been associated with slower rates of cognitive decline in a diverse cohort of older adults (Zahodne, Stern, & Manly, 2015).

Data on sex differences in PWV are limited, but several studies have suggested that differential trajectories exist with age. Women appear to display increased aortic stiffness with age, particularly with menopause. Augmented index (AI) – the interaction between the forward and reflected pulse waves that is a secondary indicator of arterial stiffness – is 7% greater in women than in men after menopause, partially because of women's shorter height and closer physical proximity between the heart and reflecting surfaces. Hayward & Kelly (1997) reported a steeper rise in PP with age in women after menopause compared to men. However, some have reported that central PWV increases with age at a greater rate in women than in men until around the age of 45, when men then increase at a greater rate (Lee & Oh, 2010; Vermeersch et al., 2008). Regarding cognitive ability, the largest sex differences are evident in motor performance between men and women (Voyer, Voyer, & Mryden, 1995). Differences on mathematical and verbal abilities approach zero, contrary to previous reporting (Linn & Petersen, 1985). The most pronounced difference between men and women in cognitive ability has been demonstrated in mental rotation of three-dimensional objects, with men outperforming women (Jäncke, 2018; Voyer, Voyer, & Mryden, 1995).

Both HR and MAP have been suggested as important adjustments to use in conjunction with measures of PWV. Amar et al. (2001) found higher HR was strongly and independently correlated with faster cfPWV. Furthermore, acute increases in HR were accompanied by reductions in arterial compliance and distensibility. Mean arterial pressure (MAP) was found to be the strongest hemodynamic predictor of PWV in a population of African American and White adults from the Georgia Stress and Heart Study (Liang et al., 2018). Within the PWV literature, adjusting for MAP is standard. However, it is important to note that the relation between PWV and blood pressure may not be linear, and is heterogeneous due to genetic background, vascular

tone and remodeling (Liang et al., 2018). Although relations of resting HR to cognitive function are unknown, a large literature reveals relations of higher blood pressure and hypertension to lower levels of cognitive function and cognitive decline (Fitri & Rambe, 2018; Tzourio, 2007; Waldstein, 2000). Furthermore, an inverted U-shaped association between MAP and cognitive outcomes may exist, wherein the minimum and maximum extremes have the greatest negative impact (Lv et al., 2017). Lastly, results of clinical trials have shown that use of antihypertensive agents is associated with decreases in PWV independent of blood pressure reduction (Asmar, 2001; Gismondi, Oigman, & Neves, 2016). Further, antihypertensive medication usage is associated with a lowered risk of cognitive decline (Gelber, Ross, Petrovich, Masaki, Launer, & White, 2013).

Both alcohol consumption and smoking habits have been linked to arterial stiffness. Greater alcoholic intake has been associated with lower levels of PWV; however, this association reversed among those with the highest alcohol consumption (15-35 glasses per week) compared to moderate alcohol consumption (10-14 glasses per week), suggesting moderate alcohol consumption as a protective factor against arterial stiffening (Sierksma et al., 2004). Similarly, in measures of cognitive outcome, moderate alcohol consumption has been associated with better cognitive performance (Kalmijn et al., 2002). However, these advantages disappear or reverse with heavy alcohol consumption, suggesting a nonlinear association (Kalmijn et al., 2002).

Smoking acutely increases PWV, augmentation index, and blood pressure in both sexes (Mahmud & Feely, 2003; Rehill, Beck, Yeo, & Yeo; 2006). Additional studies have demonstrated an increase in PWV or AI among male smokers compared to male never-smokers (Wei, Liu, & Liu, 2011). Chamberlain and colleagues (2012) demonstrated lower levels of sustained attention, working memory, and executive functioning amongst chronic smokers

without a cannabis comorbidity as compared to non-smokers. Although acute nicotine consumption may lead to immediate and temporary improvements in attention and memory, nicotine dependence and long-term heavy usage are associated with cognitive decline (Campos, Serebrisky, & Castaldelli-Maia, 2016).

Current Study & Aims

Cognitive performance in domains such as processing speed and memory often decrease with aging (Harada et al., 2013). However, it remains unclear whether cognitive decline is attributable to primary biological aging processes, or to secondary aging – the influence of age-related disease and environment (Anstey et al., 1994). Cardiovascular disease and its associated risk factors, classified as secondary aging processes, have well established negative impact on trajectories of cognitive decline (Dregan, Stewart, & Gulliford, 2013; Jefferson et al., 2015; Leritz, McGlinchey, Kellison, Rudolph, & Milberg, 2011), and are potent risk factors for MCI, Alzheimer's disease, and vascular dementia (Arvanitakis, Wilson, Bienias, Evans, Bennett & 2004; Kivipelto, Laakso, Tuomilehto, Nissinen & Soininen, 2002; Ott et al., 1998; Waldstein & Elias, 2015). Subclinical vascular disease is an intermediate pathophysiological state linking vascular risk factors and emergence of clinical CVD; it is highly predictive of incident CVD and is associated with worsened trajectories of cognitive decline (O'Donnell & Elosua, 2008; Waldstein & Elias, 2015). It is critical to better understand the relations of subclinical vascular disease to cognitive function and decline in order to improve preventative interventions for MCI and dementia.

Arterial stiffness is a form of subclinical vascular disease that increases with age and directly contributes to other cardiovascular risk factors, such as systolic hypertension (Al Hazzouri et al., 2013). PWV is considered to be the best available measure of arterial stiffness

(Al Hazzouri et al., 2013). Higher levels of and/or increases in PWV have been associated with lower levels of cognitive function and cognitive decline, particularly on cognitive screening measures (Fujiwara et al., 2005; Gasecki et al., 2013; Pase et al., 2011; Waldstein et al., 2008). However, relatively little research has investigated the relation of PWV to specific domains of cognitive function using an extensive neuropsychological battery, and no prior studies have examined a racially and socioeconomically diverse sample. Additionally, no prior research has examined race and SES as potential moderators of the relation of PWV and cognitive outcomes. Inclusion of these moderators allows potential identification of subgroups of persons who are particularly vulnerable to the impact of PWV on cognitive function. Further, additional work is needed to determine whether relations of PWV to cognitive function withstand adjustment for correlated biopsychosocial risk factors, or whether these variables serve as candidate mediators. Accordingly, this study extends the prior literature by examining potential interactive associations PWV, race, and poverty status to cognitive performance using an extensive neuropsychological battery amongst a biracial cohort of urban dwelling adults, and adjusting for potential confounders - age, education, sex, HR, MAP, cigarette and alcohol use, and antihypertensive medications. Further, sequential adjustment for depressive symptomatology and CVD risk factors - BMI, diabetes, total cholesterol, and CVD comorbidity - was examined in hierarchical regression models.

Aim 1: The first aim of the present study was to examine cross-sectional, interactive relations of PWV, self-identified race, and poverty status to cognitive function. Up to a three-way interaction was examined. Cognitive outcomes included measures in the domains of attention, working memory, verbal and nonverbal memory, perceptuo-motor speed and executive function. These models were adjusted for age, education, sex, HR, MAP, cigarette and alcohol

use, and antihypertensive medications. *A significant three-way interaction of PWV, race, and poverty status was hypothesized such that, after covariate adjustment, higher levels of PWV were associated with lower levels of cognitive performance, particularly among African Americans living in poverty.*

Aim 2: The second aim of the present study was to explore whether these associations withstand adjustments for CVD risk factors. A hierarchical model was first adjusted for depressive symptomatology, followed by a cluster of cardiovascular risk factors and comorbidities. *It was hypothesized that PWV-cognitive associations would withstand adjustments for these CVD risk factors.*

Methods

Participants

Participants were 1,899 African American (AA) and White urban dwelling adults (mean age = 48.82 years, *SD* = 9.17; 56% female; 55% African-American; 40% below the 125% poverty line) from the Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS) study from whom data on arterial stiffness and neuropsychological test performance were available. HANDLS is an epidemiological population-based longitudinal study in Baltimore City, Maryland designed to investigate race and SES related disparities in age-related health outcomes and respective influences of behavioral, psychosocial, and environmental conditions (Evans et al., 2010). Data for the proposed study were collected in wave one of HANDLS. Participant data were included if it contained at least one neuropsychological data outcome. Exclusion criteria for participation in HANDLS included: age outside 30-64 years at date of participation, pregnancy, within 6 months of undergoing active cancer treatment (chemotherapy, biologic, radiation), AIDS diagnosis, inability to provide at least 5 data points,

lack of valid picture identification, or inability to give informed consent. Exclusion from the current analyses included participants with: stroke, transient ischemic attack, dementia, other neurological disease (e.g., multiple sclerosis), history of cardiac or carotid surgeries, dialysis, heart failure, non-fasting blood draw, and missing data for covariates. The Institutional Review Board of the National Institute of Environmental Health Sciences approved the HANDLS parent study.

Measures

Sociodemographic Variables.

Poverty status (1 = income below 125% of the federal poverty threshold, 0 = income at or above 125% of the federal poverty threshold), biological sex assigned at birth (1 = male, 0 = female), and self-identified race (1 = African American, 0 = White) variables were self-reported and dichotomized. Age was a self-reported continuous variable. Education was a self-reported categorical variable reflecting the highest level completed in school.

Health Measures.

A comprehensive medical history and physical examination were performed by a study physician or nurse practitioner. Systolic and diastolic blood pressure were recorded via standard brachial artery auscultation following a 5-minute rest period. A measure was recorded on each arm and then averaged. Heart rate was obtained during the physical exam. Mean arterial pressure (MAP) was calculated as ([2 × diastolic blood pressure + systolic blood pressure] / 3). A dichotomous variable for cigarette use was coded (1 = former or current user, 0 = never smoked). A dichotomous variable for alcohol use was coded (1= former or current user, 0 = never drank). BMI was calculated as the ratio of weight (in kilograms) to height (in meters) squared. Fasting blood samples were obtained for determination of glucose and cholesterol levels. Glucose assays

were conducted at the NIA Clinical Research Branch Core Laboratory (Baltimore, MD) and Quest Diagnostics Inc. (Chantilly, VA) using a spectrophotometer (AU5400 Immuno Chemistry Analyzer; Olympus, Center Valley, PA). Fasting total cholesterol was measured enzymatically. The criteria for diabetes were: self-reported history, use of relevant medication, and/or a fasting blood glucose of ≥ 126 mg/dl. Depression symptomatology was assessed using the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). A dichotomous variable for cardiovascular comorbidity was coded to reflect a history of coronary heart disease, myocardial infarction, or peripheral arterial disease (1 = present, 0 = absent). A dichotomous variable was coded for antihypertensive medication use (1 = present, 0 = absent).

PWV Ultrasonography.

Arterial imaging was performed using a carotid doppler ultrasonogram. This non-invasive measure was obtained using a high-resolution B-mode ultrasonogram on the left carotid artery to measure systolic and diastolic arterial diameters, carotid arterial flow, intimal-medial thickness, and plaque buildup. Doppler flow probes were simultaneously placed over the carotid, brachial, and femoral pulses and gated to an electrocardiogram. The distance between the recording sites was measured externally with a tape measure. PWV between two arterial segments was calculated by dividing the distance between the two sites (m) by the time delay for the flow waves between the two sites (sec).

Cognitive Measures.

A neuropsychological battery assessed multiple domains of cognitive functioning and utilized the following tests: *Digit Span Forward (DSF) and Digit Span Backwards (DSB) subscales of the Weschler Adult Intelligence Scale-Revised (WAIS-R), Benton Visual Retention Test (BVRT), California Verbal Learning Test (CVLT), Brief Test of Attention (BTA), Trail*

Making Test part A (TMTA) and part B (TMTB), and the *Verbal Fluency Test*. As described in Strauss, Sherman, & Spreen (2006), the DSF and DSB subscales assess attention and working memory (a dimension of executive functioning). BVRT measures visual perception, constructional abilities, and nonverbal memory. CVLT measures verbal learning and memory. BTA assesses auditory divided attention. TMTA and TMTB measure attention, scanning and visuomotor tracking, cognitive flexibility (a dimension of executive functioning) and perceptuo-motor speed. The Verbal Fluency test measures language abilities and executive functioning.

In total, cognitive performance was determined by ten (10) outcome measures from the above tests: 1) number of successful trials on DSF, 2) number of successful trials on DSB, 3) errors score on the BVRT, 4) total score on the CVLT learning trials, 5) CVLT short delayed recall score, 6) CVLT long delayed recall score, 7) number of correctly monitored lists summed across both forms of the BTA, 8) time score on TBTA, 9) time score on TBTB and 10) sum of admissible words on Verbal Fluency.

WAIS-R Digit Span Forward and Backward.

The DSF subscale of the revised Weschler Adult Intelligence Scale measures attentional efficiency and the ability to focus in the presence of distracting stimuli (Lezak et al., 2012). The DSB subscale is considered a test of working memory, as it requires retaining several pieces of information and then manipulating them correctly in simultaneous processes.

DSF procedure involves the examiner reading aloud a list of numbers (one digit per second) while the participant listens, and then having the participant immediately repeat back the number list in the same order (Fink et al., 2014). Lists begin with three numbers and increase by one number for every two trials successfully completed to a maximum of nine digits. The test concludes once participants are unable to correctly complete two consecutive trials of the same

digit length. The overall DSF score is the number of trials correctly completed by the participant. DSB is administered in the same fashion but participants are asked to repeat the digit list back in the reverse order. DSB begins with a two-digit list and increases subsequently to eight-digit lengths. The overall DSB score is the number of trials correctly completed by the participant. Boone (1992) demonstrated a reliability coefficient of .81 for both DSF and DSB in a sample of psychiatric inpatients.

Benton Visual Retention Test.

The BVRT measures visual attention, constructional abilities, and nonverbal memory (Lezak et al., 2012). Three geometric shapes arranged horizontally are presented to a participant for a specified exposure time. The participant is then asked to draw the shapes from memory. Exposure time depends on the administration form being used. The number of correct responses and the number of errors were recorded. Errors include shape omission, shape distortion, shape perseverations, shape rotations, shape misplacements, or errors in size. Test-retest reliability has been found to be high for the BVRT (0.85; Sivan, 1992). Reading level had a greater influence on performance in African-Americans than level of education (Byrd, Sanchez, & Manly, 2005).

California Verbal Learning Test.

The CVLT test measures episodic verbal learning and memory. A fixed order list of 16 nouns (List A) is read aloud to the participant in one-second intervals. Participants immediately recall as many words as possible. This process is repeated five times. In the HANDLS study, only the first three learning trials were completed. A second list of 16 words (List B) is then introduced as interference and free recall and cued recall of List A is queried (short delay recall). This is followed by a 20-minute delay during which nonverbal tests may be administered. Free and cued recall is then repeated (long delay recall), followed by a 44-item recognition task where

the participant must indicate whether a word was on the original list or is a distractor (Delis et al., 1988). In the HANDLS study, the cued recall trials were omitted. CVLT performance was recorded as the total score for the immediate recall trials of List A, total score for short delay recall, and total score for the long delay recall.

Woods et al. (2006) demonstrated medium to high test-retest reliability (0.80 – 0.84) for trials 1-5, short recall, and long recall trial of the CVLT. Demographic characteristics, particularly age, have been shown to contribute to test performance in African Americans to a greater extent than in Whites (Norman et al., 2011). Additionally, reading ability was a significant predictor in CVLT performance amongst low-SES African Americans and Whites, as well as high-SES African Americans (Dotson et al., 2009).

Brief Test of Attention.

The BTA is a measure of divided attention on a task that is presented verbally (and designed to reduce confounds of motor speed, visual scanning, and memory from task requirements). Additionally, the test is designed to detect attentional impairments (Strauss, Sherman, & Spreen, 2006). Participants are administered two, 4-minute forms presented on an audio cassette tape. On the first form (Form N), a voice recites 10 lists of numbers and letters (read at one item per second) that increase in length from 4 to 18 items. Participants are told to ignore the letters and to count how many numbers are read on each list. Each list is followed by 5 seconds of silence during which the participant reports their answer. The same 10 lists are repeated in the next form (Form L), during which participants are told to count how many letters are read on each list (Schretlen, Bobholz, & Brandt, 1996).

Internal consistency for the BTA was determined to be .82. Correlation between the two forms increased from .69 to .81 after combining the normal and clinical participants in the

original test construction sample (Schretlen, Bobholz, & Brandt, 1996). In its original development, age and education were found to be significantly associated with BTA scores. No ethnic differences were found for BTA performance between African Americans and Whites, and when regressed on age, sex, race, and education, only age accounted for significant variance in performance amongst normal adults (Schretlen, Bobholz, and Brandt, 1996). Additional studies have suggested that gender has an impact on BTA performance, where women perform slightly better than men by approximately 0.8 points (Schretlen, Bobholz, and Brandt, 1996).

Trail Making Test.

The TMT is a measure of attention, perceptuo-motor speed, and mental flexibility. The test consists of two, timed parts, part A and part B. Both parts require visual tracking of a sequence and speeded performance, but part B additionally requires divided attention. In part A, participants are told to connect with a pencil 25 encircled numbers randomly distributed on a page. In part B, participants connect 25 encircled numbers and letters in alternating order. Both part A and part B are prefaced with an untimed demonstration where the participant becomes accustomed to the trials and corrects any mistakes made. Outcome measures include time to completion in seconds and number of mistakes committed. Timing continues even when participants commit mistakes (Strauss et al., 2006). For analysis, all values exceeding 300 seconds on TMTB were changed to a 300 sec. maximum, as this cutoff has been suggested for discontinuing test administration (Bowie & Harvey, 2006).

Age, education, and ethnicity have been shown to be determinants in TMT outcomes. Increasing age is associated with declining performance on TMTA and TMTB, specifically the time it takes to complete the test. Lower levels of educational attainment are associated with poorer test scores. African Americans who speak “Black English,” or those not accustomed to

timed academic structure, have been found to take longer to complete TMTB due to lack of saliency of a timed task within traditional African American culture (Strauss et al., 2006). Within normal populations, test-retest reliability has ranged from .46 for part A in Bornstein et al. (1987), to .89 for part B in Dikmen et al. (1999). Better test-retest reliability for part A (0.78) was found by Wagner, Helmreich, Dahmen, and Tadic (2011).

Verbal Fluency.

The test of Verbal Fluency measures semantic fluency and the spontaneous production of words in a given category within a minute. The subject must quickly produce as many words as possible from within a particular category. HANDLS utilized the semantic category of animals. Scores on this task were the sum of admissible animal words and did not include preservations, proper nouns, variations of animal names, or errors. This measure tests the search strategies of the subject, as well as set shifting and word retrieval ability. Set shifting is the subject's ability to efficiently switch between naming clusters (Troyer, Moscovitch, & Winocur, 1997). Deficits on this test may be indicative of gaps in knowledge, low executive functioning, or inefficient search strategies.

Low educational attainment is strongly linked to Verbal Fluency performance. Crossley, Darcy, & Rawson (1997) demonstrated that those with the highest education level (more than 13 years) were able to produce twice as many words than those in the lowest education level. White ethnicity is associated with higher test scores in comparison to minorities, and performance shows a mild decline in old age (Delis, Kaplan, & Kramer 2001; Strauss et al., 2006). Test-retest reliability ranges from .70 to .88 (Spreen & Strauss, 1998).

Data Analysis

Power Analysis.

G*Power statistical software 3.1.9.3 was used for the power analysis of the proposed study. These estimates were based on an F-Test linear multiple regression: Fixed model, R^2 increase analysis. A sample size of 1899 and test of 20 total predictors (PWV, race, poverty status, Sex, Age, Education, MAP, HR, Alcohol Status, Smoking Status, Depression, BMI, Diabetes, Cholesterol, CVD history, Antihypertensive medication, race × poverty status, PWV × poverty status, PWV × race, PWV × race × poverty status) was used. For a small effect size to be detected (f^2 estimate of 0.02), using an $\alpha = 0.05$, a power of .99 was achieved.

Descriptive Statistics.

Descriptive statistics of variables collected in wave 1 were computed. Normality, skewness, outliers, and multicollinearity were examined for all variables. Raw scores were used for the analysis and distributions were inspected via histograms. Any skewed distributions were log-transformed to achieve normality. Zero-order correlations were then computed among variables.

Examining Moderation.

The Statistical Package for the Social Science (SPSS) Version 25.0 and the PROCESS macro were utilized to perform hierarchical regression analysis to construct models of the interactive relations of PWV × race × poverty status (and all associated two-way interactions and main effects) on cognitive performance. If the three-way interaction was not significant, backwards elimination was performed by removal of the interaction term. This was followed by elimination of two-way interactions if none were found to be significant. In the absence of significant three-way interactions, significant two-way interactions and/or main effects were

interpreted. Cognitive performance was defined by ten outcome measures from the series of neuropsychological assessments described above (DSF, DSB, BVRT Total Errors, CVLT Total Score, CVLT Short Delay Recall, CVLT Long Delay Recall, BTA, TMTA, TMTB, Verbal Fluency). All models included the following adjustment variables: age, education, sex, MAP, HR, alcohol use, cigarette use, and antihypertensive medications. In the second step of the hierarchical regression models, depressive symptoms were entered to explore whether any significant findings from Model 1 were rendered non-significant. In the third step of the hierarchical model, the following adjustment variables were entered: BMI, diabetes, total cholesterol, and CVD comorbidity. Thus, the hierarchal regression models occurred in three steps:

Step 1) Moderation model including PWV, race, poverty status, PWV × race, PWV × poverty status, race × poverty status, PWV × race × poverty status with adjustments for age, sex, education, alcohol use, cigarette use, MAP, HR, and hypertensive medication.[1]

Step 2) Moderation model from Step 1 + Depressive Symptomatology

Step 3) Moderation model from Step 2 + BMI + Diabetes + Total Cholesterol + CVD history

If any PWV-cognitive associations were rendered non-significant in steps 2 or 3, findings were examined using the SPSS PROCESS macro to evaluate the potential presence of mediation or moderated mediation. For mediational analysis, both direct and indirect effects were examined. For indirect effects, bootstrapping confidence intervals (CI) were performed with 5000 samples. All hypotheses were evaluated using null hypothesis significance testing with an alpha level at .05 level. Predictors with a $p < .05$ were deemed significant, and all reported

[1] Step 1 was additionally conducted in a three-step permutation: 1) covariates of age, sex, education, alcohol, cigarette, 2) covariates of MAP and HR added in, 3) covariate of hypertensive medication added in. This permutation (data not shown) yielded the same results as simultaneous entry of the covariates.

coefficients are unstandardized. Effect sizes were calculated for all significant findings using adjusted R^2.

Results

Preliminary Analysis

Preliminary data screening was performed via Q-Q plots and histograms to determine whether any outcome variables violated the assumption of normality. Performance on both Trail Making Tests A and B suggested a highly and positively skewed distribution. Thus, a logarithmic transformation was applied to the TMT A and B outcomes. Normality was deemed to be sufficient after transformation, and all related multivariable regression analysis included these log-transformed outcome variables. Normality on all other outcome variables was deemed acceptable.

Descriptive Statistics

The cohort included 1,899 participants who met stated inclusion criteria for the current study. A majority of the sample was female (55.7%, n = 1057) and African American (55.3%, n = 1050). Additionally, 60.3% of the sample was classified as living above the poverty line (n = 1146). The age of sample participants ranged from 30 to 64 years (M = 48.82, SD = 9.17). Approximately 48.1% of the sample were diagnosed as hypertensive (n = 914), however only 32.1% reported having a prescription for antihypertensive medications (n = 610). The sample was largely overweight or obese, with 72.5% of participants having a BMI greater than 25 kg/m^2 (n = 1377). Table 1 presents sample characteristics for sociodemographic variables, predictors, and covariates. Tables 2 and 3 presents bivariate correlations among the study's variables.

Differences in predictor, covariate, and outcome variables as a function of race and poverty status

African American and White participants differed significantly with respect to pulse wave velocity, mean arterial pressure, fasting glucose level, poverty status, antihypertensive medication usage, and on multiple cognitive endpoints. Specifically, African Americans exhibited greater PWV ($t(1897) = -2.41$, $p = .016$), higher MAP ($t(1897) = -2.91$, $p = .004$), and lower fasting glucose levels ($t(1897) = 2.90$, $p = .004$) than Whites. African Americans were more likely than Whites to live in poverty ($X^2(1) = 26.59$, $p < .001$) and to be prescribed antihypertensive medication ($X^2(1) = 13.17$, $p < .001$). On cognitive outcomes, African Americans scored lower than Whites on DSF ($t(1694.48) = 6.50$, $p < .001$), DSB ($t(1612.51) = 10.34$, $p < .001$), CVLT Total Score ($t(1371.53) = 6.62$, $p < .001$), CVLT Short Delay Recall ($t(1367.95) = 7.86$, $p < .001$), CVLT Long Delay Recall ($t(1360.10) = 8.34$, $p < .001$), BTA ($t(1897) = 7.952$, $p < .001$), Verbal Fluency ($t(1683.64) = 6.53$, $p < .001$), and had longer completion times on TMTA ($t(1897) = -8.47$, $p < .001$) and TMTB ($t(1832.58) = -11.93$, $p < .001$), and higher total errors on BVRT ($t(1861.70) = -2.82$, $p = .005$).

Significant differences were further observed as a function of poverty status classification for age, PWV, education level, depression symptomatology, BMI, racial identity, alcohol usage, and cigarette usage, and multiple cognitive outcomes. As compared to those above poverty, persons living in poverty were, on average, younger ($t(1897) = 2.20$, $p < .001$), had lower PWV ($t(1897) = 2.27$, $p = .023$), had lower levels of education ($t(1644.76) = 10.67$, $p < .001$), endorsed more depressive symptoms ($t(1897) = -6.52$, $p < .001$), had lower levels of BMI ($t(1897) = 2.42$, $p = .016$), were more likely to be African American ($X^2(1) = 26.59$, $p < .001$), were slightly less likely to have used alcohol in the past ($X^2(1) = 8.36$, $p = .004$), and were more likely to have

smoked in the past ($X^2(1) = 4.38$, $p = .036$). On cognitive outcomes, on average, those living in poverty scored lower than those above poverty on DSF ($t(1897) = 5.78$) $p < .001$), DSB ($t(1897) = 6.63$, $p < .001$), CVLT Total ($t(1897) = 4.62$, $p < .001$), CVLT Short Delay Recall ($t(1897) = 3.91$), $p < .001$), CVLT Long Delay Recall ($t(1414.76) = 3.75$, $p < .001$), BTA ($t(1348.52) = 6.18$, $p < .001$), Verbal Fluency ($t(1669.69) = 6.44$, $p < .001$), and had longer completion times on TMTA ($t(1897) = -5.54$, $p < .001$) and TMTB ($t(1461.36) = -7.26$, $p < .001$). Additionally, those in poverty were more likely to have greater total errors on the BVRT ($t(1472.80) = -4.09$, $p < .001$).

Hierarchical Regression Models: Test of Primary Study Aims

As stated previously, the present study had two primary aims. The first aim was to investigate the interactive relations of PWV, self-identified race, and poverty status in predicting cognitive outcomes within the domains of attention, executive functioning, memory, and perceptuo-motor speed after adjustment for age, sex, education, alcohol use, cigarette use, MAP, HR, and antihypertensive medication. The second aim explored whether the noted significant associations among PWV, race, and poverty status withstood additional hierarchical adjustments for depression symptoms, and cardiovascular risk factors and diseases. Hierarchical regression modeling was conducted on 10 cognitive function outcomes (DSF, DSB, BVRT total errors, CVLT Total Score, CVLT Short Delay Recall, CVLT Long Delay Recall, BTA, TMTA, TMTB, and Verbal Fluency) with moderators of race (moderator 1) and poverty status (moderator 2; see Figures 1-3). If the three-way interaction term was found to be non-significant, it was removed from the model in order to examine all two-way interactions. If no significant two-way interactions were found, they were taken out of the model to test for significant main effects of PWV.

Hypothesis 1.

It was hypothesized that the interaction of PWV, race, and poverty status would be significantly associated with cognitive performance such that the association of elevated levels of PWV with lower cognitive outcomes would be most pronounced among African Americans living in poverty. Results of this first step of the hierarchical regression analyses are reported below for each outcome measure.

WAIS – R Digit Span Forward.

Table 4 demonstrates the results of hierarchical regression for the interactive associations of PWV, race, and poverty status on DSF. Results revealed no significant three-way interaction among these variables in the base model after adjustments for age, sex, education, alcohol use, cigarette use, MAP, HR, and antihypertensive medication (B = -.06, t(15, 1624) = -.56, p > .05). After elimination of the three-way interaction, there were no significant two-way interactions of PWV and race (B = -.00, t(12, 1627) = -.08, p > .05) or PWV and poverty status (B = .07, t(12, 1627) = 1.39, p > ,05) on DSF. After elimination of these two-way interactions, there were no significant main effects of PWV on DSF (B = .02, t(11, 1628) = .64, p > .05).

WAIS-R – Digit Span Backwards.

Table 5 demonstrates the results of hierarchical regression for the interactive associations of PWV, race, and poverty status on DSB. Results revealed no significant three-way interaction among these variables in the base model following adjustments (B = -.03, t(15, 1619) = -.28, p > .05). After elimination of the three-way interaction, there were no significant two-way interactions of PWV and race (B = -.02, t(12, 1622) = -.51, p > .05) or PWV and poverty status

(B = .02, t(12, 1622) = .46, p > .05) on DSB. After elimination of these two-way interactions, there were no significant main effects of PWV on DSB (B = .01, t(11, 1623) = .60, p > .05).

Benton Visual Retention Test Total Errors.

Table 6 demonstrates the results of the hierarchical regression for the interactive associations of PWV, race, and poverty status on BVRT total error score. Results revealed no significant three-way interaction among these variables in the base model following adjustments (B = .22, t(15, 1668) = .98, p > .05). After elimination of the three-way interaction, there were no significant two-way interactions of PWV and race (B = .11, t(12, 1671) = 1.13, p > .05) or PWV and poverty status (B = -.08, t(12,1671) = -.69, p > .05) on BVRT total error score. After elimination of these two-way interactions, there were no significant main effects of PWV on BVRT total errors (B = .09, t(11, 1672) = 1.66, p > .05).

California Verbal Learning Test Total Recall.

Table 7 demonstrates the results of the hierarchical regression for the interactive associations of PWV, race, and poverty status on CVLT Total Score. Results revealed no significant three-way interaction among these variables in the base model following adjustments (B = -.26, t(15, 1382) = -.90, p > .05). After elimination of the three-way interaction, there were no significant two-way interactions of PWV and race (B = -.05, t(12, 1385) = -.42, p > .05) or PWV and poverty status (B = .27, t(12, 1385) = 1.91, p > .05) on CVLT Total Score. After elimination of these two-way interactions, there were no significant main effects of PWV on CVLT Total Score (B = .06, t(11, 1386) = .95, p > .05).

California Verbal Learning Test Short Delay Recall.

Table 8 demonstrates the results of the hierarchical regression for the interactive associations of PWV, race, and poverty status on CVLT Short Delay Recall Score. Results

revealed no significant three-way interaction among these variables in the base model following adjustments (B = -.12, t(15, 1356) = -.91, p > .05). After elimination of the three-way interaction, there were no significant two-way interactions of PWV and race (B = -.05, t(12, 1359) = -.79, p > .05) or PWV and poverty status (B = .03, t(12, 1359) = .52, p > .05) on CVLT Short Delay Recall Score. After elimination of these two-way interactions, there were no significant main effect of PWV on CVLT Short Delay Recall Score (B = .05, t(11, 1360) = 1.59, p > .05).

California Verbal Learning Test Long Delay Recall.

Table 9 demonstrates the results of the hierarchical regression for the interactive associations of PWV, race, poverty status on CVLT Long Delay Recall Score. Results revealed no significant three-way interaction among these variables in the base model following adjustments (B = -.21, t(15, 1357) = -1.54, p > .05). After elimination of the three-way interaction there were no significant two-way interaction of PWV and race (B = .01, t(12, 1360) = .17, p > .05). There was, however, a significant two-way interaction of PWV and poverty status (B = .14, t(12, 1360) = 2.21, adjusted R^2 = .18, p = .028), such that, among those living in poverty, individuals with faster PWV displayed higher scores on this test (p = .009). Figure 5 displays this interaction plot.

Brief Test of Attention.

Table 10 demonstrates the results of the hierarchical regression for the interactive associations of PWV, race, and poverty status on BTA scores. Results revealed a significant three-way interaction among these variables in the base model after adjustments (B = -.32, t(15, 1411) = -3.03, adjusted R^2 = .11, p = .002). Among Whites, but not African Americans, living in poverty, faster PWV was associated significant with higher BTA scores among those living in poverty (p < .05). PWV and BTA scores were not associated significantly among Whites living

above the poverty threshold, or African Americans (irrespective of poverty status; *p's* > .05). Figure 6 displays this interaction plot.

Trails Making Test Part A.

Table 11 demonstrates the results of the hierarchical regression for the interactive associations of PWV, race, and poverty status on TMTA completion time. Results revealed no significant three-way interaction among these variables in the base model following adjustments (B = -.01, t(15, 1643) = -1.50, p > .05). After elimination of the three-way interaction there were no significant two-way interactions of PWV and race (B = .00, t(12, 1647) = .46, p > .05) or PWV and poverty status (B = -.00, t(12,1647) = -.40, p > .05) on TMTA completion time. Upon elimination of these two-way interactions, there were no main effects of PWV on TMTA completion time (B = .00, t(11, 1648) = -.03, p > .05).

Trail Making Test Part B.

Table 12 demonstrates the results of the hierarchical regression for the interactive associations of PWV, race, and poverty status on TMTB completion time. Results revealed no significant three-way interaction among these variables in the base model following adjustments (B = .01, t(15, 1633) = .72, p > .05). After the elimination of the three-way interaction there were no significant two-way interactions of PWV and race (B = .01, t(12, 1636) = 1.03, p > .05) or PWV and poverty status (B = -.00, t(12, 1636) = -.27, p > .05) on TMT B completion time. Eliminating these two-way interaction revealed no significant main effects of PWV (B = -.00, t(11, 1637) = -1.15, p > .05) on TMT B completion times.

Verbal Fluency.

Table 13 demonstrates the results of the hierarchical regression for the interactive associations of PWV, race, and poverty status on Verbal Fluency. Results revealed no significant

three-way interaction among these variables in the base model following adjustments (B = -.13, t(15, 1657) = -.58, p > .05). After eliminating the three-way interaction variable, there was no significant two-way interaction of PWV and race (B = .13, t(12, 1660) = 1.23, p > .05). However, there was a significant two way interaction of PWV and poverty status (B = .22, t(12, 1660) = 1.99, adjusted R^2 = .13, p = .047) on Verbal Fluency score such that, among those living in poverty, higher PWV was associated with higher Verbal Fluency scores (p = .006). Figure 7 displays this interaction plot.

Hypothesis 2.

As stated previously, the second aim of the study examined whether significant associations between PWV, race, and poverty status on cognitive outcomes withstood additional adjustments of depressive symptoms and cardiovascular risk factors. From hypothesis one, the significant base models for CVLT Long Delay Recall (PWV × poverty status), BTA (PWV × race × poverty status), and Verbal Fluency (PWV × poverty status) were retained and used as step one in the originally proposed hierarchal procedure. Step two added in the covariate of depression symptomatology (as measured by the CES-D), while the final step added covariates of body mass index (BMI), diabetes diagnosis, total fasting glucose levels, and history of cardiovascular disease. Moderated mediation analysis was conducted if any of the models became non-significant in steps 2 or 3.

California Verbal Learning Test Long Delay Recall.

Table 14 demonstrates the hierarchal entry of covariates and associated coefficients for the previously noted interaction of PWV and poverty status on CVLT Long Delay Recall. The PWV and poverty status interaction remained significant through step 3 (B = .15, t(18, 1354) = 2.32, p = .021).

Brief Test of Attention.

Table 15 demonstrates the hierarchal entry of covariates and associated coefficients for the previously noted interaction of PWV, race, and poverty status on BTA scores. The three-way PWV, race, and poverty status interaction term remained significant through step 3 (B = -.30, t (21, 1405) = -2.91, $p > .05$).

Verbal Fluency.

Table 16 demonstrates the hierarchal entry of covariates and associated coefficients for the previously noted interaction of PWV and poverty status on Verbal Fluency scores. The two way PWV and poverty status interaction term became non-significant at step 2 (B = .34, t(12, 1660) = 1.99, $p > .05$).

Because the PWV × Poverty Status interaction became non-significant at step two, a moderated mediation model was used to investigate whether depressive symptomatology mediated the relation between PWV and Verbal Fluency, and whether this association was moderated by poverty status. This moderated mediation model examined the indirect effect of PWV on Verbal Fluency scores via depressive symptomatology (as measured by the CES-D scale) with a moderator of poverty status and all relevant covariates (age, sex, race, education, alcohol use, cigarette use, MAP, HR, and antihypertensive medication use). The SPSS macro PROCESS template model 59 was utilized in this analysis. Figure 4 illustrates the conceptual diagram of the moderated mediation analysis with Verbal Fluency as the outcome variable. Figure 5 illustrates the simplified statistical path model of the moderated mediation analysis for the following results. With CES as the outcome variable, PWV (a_1 = -.06, t(1673) = -.46, $p >$ .05), poverty status (a_2 = .50, t(1673) = .26, $p > .05$), and their interaction (a_3 = .19, t(1673) =

.79, $p > .05$, LLCI = -.28, ULCI = .65) were not associated with the mediating variable. When controlling for PWV, CES was significantly associated with Verbal Fluency (b_1 = -.04, $t(1659)$ = -2.89, $p < .01$), as was poverty status (c_2' = -3.43, $t(1659)$ = -3.43, $p < .01$). However, the interaction of CES and poverty status on Verbal Fluency was not significant (b_2= .02, $t(1659)$ = 1.05, $p > .05$). The estimated direct effect of PWV on Verbal Fluency while controlling for CES and poverty status, c_1' = -.02, $t(1659)$ = -.37, $p > .05$, LLCI = -.14, ULCI = .10, was not significant. However, the interaction term of PWV and poverty status on Verbal Fluency was significant (c_3 = .26, $t(1659)$ = 2.34, p = .02). The index of the indirect effect of the moderated mediation was -.01 with the lower and upper limits being -.02 and .01, respectively. As the bootstrapped CI (95%) of this index did include zero, this moderated mediation was not considered significant. Figure 8 displays these results.

Discussion

This study, to my knowledge, was the first to investigate the interactive associations of PWV, race, and poverty status to neuropsychological outcomes spanning multiple cognitive domains within a sample of biracial urban-dwelling adults. Within Aim 1, significant three-way interactions amongst these variables were hypothesized such that negative influences of PWV on cognitive outcomes would be most evident among African Americans living in poverty. If no significant three-way interactions were present, it was posited that significant two-way interactions would demonstrate negative PWV and cognitive function relations most evident in African Americans and in those living in poverty. In the absence of two-way interactions, additional backwards elimination was expected to yield significant main effects of PWV wherein elevated PWV would significantly predict lower performance on cognitive measures. Next, in Aim 2, it was hypothesized that any significant relations of PWV, race, and poverty status to

cognitive function found in Aim 1 would withstand hierarchical adjustments for depressive symptomatology and cardiovascular risk factors and comorbidities.

Results from these analyses did not support the stated hypotheses. No significant interactive or independent associations of PWV were noted with respect to seven of the 10 cognitive outcome variables – Digit Span Forward, Digit Span Backwards, BVRT Total Errors, CVLT Total Recall, CVLT Short Delay Recall, Trail Making Test Part A, and Trail Making Test Part B. Although several significant interactions were found for three of 10 cognitive outcomes - three-way associations of PWV, race, and poverty status on BTA, and two-way associations of PWV and poverty status on CVLT Long Delay Recall and Verbal Fluency – the associations were directionally opposite to those posited. Specifically, higher levels of PWV were associated with better BTA performance (which reflects complex and divided attention) among Whites living in poverty. Further, regardless of race, greater PWV was related to better performance on CVLT Long Delay Recall, a test of verbal memory, and Verbal Fluency, a test of verbal abilities and executive functioning, among those living in poverty. After adjustment for depressive symptomatology and CVD risk factors and comorbidities, the findings for CVLT Long Delay Recall and BTA remained significant. However, the interactive relation of PWV and poverty status on Verbal Fluency became non-significant with the addition of depression as a covariate. Subsequent moderated mediation analysis revealed no significant indirect effects of depressive symptomatology on the interactive relation of PWV and poverty status to Verbal Fluency. Below, I will discuss these findings in greater detail for each study aim. I will first discuss the null findings followed by the several significant counter-intuitive findings.

Relative Absence of Interactions & Main Effects of PWV, Race, and Poverty Status on Cognition (Aim 1)

The present study revealed mainly null findings, with seven of 10 cognitive outcomes unrelated to PWV and its interaction with race and poverty status. Due to the predominance of these non-significant findings, the current results may reflect a true lack of interactive relation among these predictor variables and performance on select tests of attention, executive functioning, verbal and non-verbal memory, and perceptuo-motor speed within the current sample. This interpretation is supported by the study's statistical power to detect a small effect size. Further, it is possible that the three significant interactive associations of PWV, race, and/or poverty status noted were spurious (although alternative explanations are considered below). Because this was the first study to examine the interactive relations of PWV, race, and poverty status to multiple domains of cognitive function using a comprehensive neuropsychology battery, the present findings are difficult to reconcile with previous literature.

It was hypothesized that moderation of PWV by race and poverty status would reveal that historically disenfranchised populations – particularly African Americans living in poverty - would be vulnerable to deleterious PWV-cognition associations, at least in part due to their disproportionate cumulative exposure to environmental and interpersonal stressors. Furthermore, it has previously been demonstrated that PWV varies by both race and SES wherein individuals of marginalized races and of low SES are more likely to have greater PWV (Birru et al., 2011; Heffernan et al., 2007; Goel et al., 2017; Kim et al., 2020; Morris et al., 2013; Thurston & Matthews, 2009; Trudel et al., 2016). For example, in a biracial sample of urban-dwelling adults, group differences revealed that African Americans displayed higher PWV compared to Whites, and that this difference remained after adjustment for history of hypertension, smoking status,

BMI, MAP glucose, age, and gender (Morris et al., 2013). Similar disparities are seen in literature pertaining to cognitive performance indicating that traditionally disenfranchised and marginalized groups tend to show lower test scores (Glymour & Manly, 2008; Mehta et al., 2004). Previous work has shown that, on average, African Americans score less well than Whites on select tests of word retrieval (Lichtenberg, Ross, & Christensen, 1994), attention and working memory (Werry, Daniel, & Bergstrom, 2019), perceptuo-motor speed and cognitive flexibility (Werry et al., 2019), and verbal memory (Werry et al., 2019). Such differences have been eliminated when ethnic-based norms are applied (Werry et al., 2019), and may be partially attributed to evident racial differences in quality of educational attainment (Glymour & Manly, 2008). Nonetheless, these disparities emphasize the embedded inequalities that differentially impact the cardiovascular and cognitive health of African Americans as well as those of lower SES and continue to justify further examination of my hypothesis that individuals of these sociodemographic groups may be more vulnerable to the negative impact of greater PWV on cognitive performance. Despite the predominantly null, and few counter-intuitive results in the present sample, this applicable reasoning stresses the importance of continued work on potentially deleterious influence of PWV on cognitive functioning among marginalized populations.

Despite the relative absence of sociodemographic moderation, results of prior literature would have nonetheless led us to expect a significant main effect of PWV on cognitive performance even in the absence of effect modification. In that regard, a recent meta-analysis conducted by Alvarez-Bueno et al. (2020) pooled literature on PWV-cognition relations to assess the strength of cross-sectional and longitudinal associations across study designs. Results indicated that the cognitive domains of executive function and memory, as well as global

cognition, were negatively impacted by PWV. These associations were maintained after adjustment for demographic variables (age, sex, education level), clinical factors (BMI, systolic blood pressure, diastolic blood pressure, depression level), and assessment characteristics (type of PWV measurement and type of device used; Alvarez-Bueno et al., 2020). Yet, 18 of the 38 studies included in the meta-analysis utilized a cognitive screening test (i.e., MMSE, Modified MMSE [3MS], Montreal Cognitive Assessment [MOCA]) as the outcome variable. So, while a cumulative review of the literature highlights the deleterious impact of PWV on cognition, the wide usage of brief cognitive screeners makes many of these results minimally applicable to the current study.

With respect to the prior studies that utilized clinical neuropsychological measures, the present investigation had adequate overlap with respect to cognitive domains assessed. However, there was only partial overlap among the specific cognitive tests used (Alvarez-Bueno et al., 2020). In that regard, only five of the 10 outcome measures used herein could be commonly found in the prior PWV-cognition literature: the Verbal Fluency test, TMT-A and TMT-B, and DSF and DSB (Abbatecola et al., 2008; Elias et al., 2009; Hajjar et al., 2016; Kim et al., 2017; Lamballais et al., 2018; Mitchell et al., 2011; Muela et al., 2018; Muller et al., 2007; Palta et al., 2019; Pase et al., 2016; Poels et al., 2007; Singer et al., 2013; Tsao et al., 2013). Furthermore, nearly all of these studies (apart from Lamballais et al., 2018) used a combination of measures to construct a composite score as an index of executive functioning. The Lamballais et al. (2018) study used raw scores to tabulate the g-factor, a measure of global cognition. It is conceivable that the results of the current study may have been different if similar cognitive composite scores were analyzed as opposed to my use of scores on individual tests.

Only two prior studies investigated the relation of PWV to performance on select individual cognitive tests (Elias et al., 2009; Kim et al., 2017). Elias et al. (2009) reported a significant association between greater cfPWV and lower performance on the Similarities subtest of the WAIS. Kim and colleagues (2017) found that higher PWV was associated with longer completion times on both parts A and B of the Trail Making Test. However, these associations were rendered non-significant after adjustments for demographic factors, the Charlson comorbidity index, systolic blood pressure, and baseline reading score (Kim et al., 2017). As noted above, the remaining studies grouped cognitive outcomes into larger composite scores representative of cognitive domains (Abbatecola et al., 2008; Hajjar et al., 2016; Lamballais et al., 2018; Mitchell et al., 2011; Muela et al., 2018; Muller et al., 2007; Palta et al., 2019; Pase et al., 2016; Poels et al., 2007 Singer et al., 2013; Tsao et al., 2013). While composite measures make it easier to categorize general cognitive patterns and domains, it prevents the examination of more specific cognitive subdomains. Unique information assessed by each test may be lost by using such composite scores. It is for this reason we examined scores on individual tests as outcome variable in the present investigation.

There were several additional methodological differences between the present study and prior literature. First, the mean age of participants in the present study is considerably lower (M = 48.82, SD = 9.17, range 30.0 – 64.1) compared to much of the prior literature that included samples with a mean age of 70 years or older (Abbatecola et al., 2008; Benetos et al., 2012; Fujiwara et al., 2005; Fukuhara et al., 2006; Hanon et al., 2005; E. D. Nilsson et al., 2014; Scuteri et al., 2014; Scuteri et al., 2007; Tsao et al., 2013; Zhong et al., 2014). Fewer studies have aimed to elucidate the midlife association of PWV and cognition (Al Hazzouri et al., 2015; Hajjar et al., 2016; Pase et al., 2016). A mid-life sample is less likely to display cognitive

difficulties as compared to an elderly population. Furthermore, PWV levels tend to increase with advancing age (particularly after the age of 50 years); thus, it is possible that the relatively younger sample limited the ability to detect the negative downstream consequences of elevated PWV (Mitchell et al., 2004). In that regard, the present sample also lacked a high proportion of individuals with a clinically high PWV value. Only 85 individuals (4.5% of the sample) had PWV equal to or above 12 m/s, a value that has been posited in the literature as a threshold above which blood velocity begins to detrimentally impact downstream tissue integrity (Scuteri & Wang, 2014; Zhong et al., 2014). Previous literature on PWV-cognition has commonly demonstrated sample averages above 10 m/s for PWV (Benetos et al., 2012; Cooper et al., 2016; Elias et al., 2009; Fukuhara et al., 2006; Kim et al., 2009; Poels et al., 2007; Scuteri et al., 2007). In the present study the average PWV of 8.1 m/s was considerably lower than that seen in past work and is well below the clinical threshold for detrimental downstream consequences (and therefore perhaps cognitive correlates). In addition, given prior findings of non-linear relations of PP (an indirect index of arterial stiffening) to cognitive function (McDade et al., 2016), it is possible that similar associations would be noted in the present sample given the predominantly normal range of PWV.

Next, the present study's sample was considerably more diverse than most samples used in previous research. Demographic characteristics of the samples used in previous PWV-cognition studies were largely White, male, and living above the poverty line (Alvarez-Bueno et al., 2020). In contrast, the current study sample was 60.4% African American, 55.7% female, and with 39.7% living below the poverty line. These differences may help to explain the disparities in the results of the current study and previous literature. The limited past work with diverse samples examined the relation of PWV to MCI or dementia prevalence (Meyer et al., 2017;

Hughes et al., 2018). Interestingly, Meyer et al. (2017) demonstrated a strong link between elevated PWV, BP, and central PP and higher incidence of MCI and dementia among Whites with much weaker associations among African Americans. These racial differences, however, were not found in Hughes et al. (2018).

It warrants mentioning that results of prior PWV-cognition studies have not been consistent in revealing lower levels of cognitive function with greater arterial stiffening. Singer et al. (2013) investigated cross-sectional associations between cfPWV and cognitive test scores. When using PWV as both a continuous or categorical variable, linear regression revealed no relation of PWV to composite global cognition levels, processing speed, memory, visuo-spatial ability, or executive function (Singer et al., 2013). These null findings were attributed to a more comprehensive list of covariates employed and the use of Bonferroni correction for multiple comparisons. Similarly, the present study applied a comprehensive list of adjustment variables. Further, as noted above, results of select studies have revealed non-linear relations of PP with cognitive function such that moderate range values were associated with the best cognitive performance (McDade et al., 2016).

In sum, there are multiple methodological issues that may partially explain the inconsistency of the present findings with those from the prior PWV-cognition literature. These include the heterogeneity of cognitive domains and tests used as outcome measures, as compared to the common use of cognitive screening measures and composite test scores (Al Hazzouri et al., 2013; Benetos et al., 2012; Fujiwara et al., 2005; Scuteri et al., 2005; Sugawara et al., 2010; Taniguchi et al., 2015); substantially different sample characteristics including much younger age range and greater sociodemographic diversity than in prior work (Benetos et al., 2012; Dixon et al., 2020; Fujiwara et al., 2005; Rouch et al., 2018; Scuteri et al., 2005; Waldstein et al., 2008;

Zhong et al., 2014) and a mean value for PWV that is well within the clinically normal range. Lastly, there was no standard set of adjustment variables used across investigations. All of these factors may have contributed to the differential findings of the present study when compared to prior literature. Nonetheless, the present analyses did reveal several significant associations of PWV to cognitive function that are discussed below.

Significant Interactions of PWV, Race, and Poverty Status on Cognition (Aim 1)

As previously noted, review of the literature regarding PWV and cognition would suggest associations of elevated PWV with lower levels of cognitive function. Although several significant associations among PWV, poverty status, and race were found in the current study, the direction of these associations were counter to my hypotheses and the general body of literature (Al Hazzouri et al., 2013; Alvarez-Bueno et al., 2020; Benetos et al., 2012; Fujiwara et al., 2005; Scuteri et al., 2005; Sugawara et al., 2010; Taniguchi et al., 2015; Waldstein et al., 2008). Specifically, the present findings revealed a significant interaction of PWV and poverty status on CVLT Long Delay Recall and Verbal Fluency, such that among those living in poverty, higher PWV was associated with better performance on the measures. Additionally, I found a significant three-way interaction among PWV, race, and poverty status on BTA such that higher PWV was associated with better performance among White individuals living in poverty. It is worth mentioning that the number of analyses conducted in this study elevates the risk of Type I error, creating the need to interpret these findings with caution.

The findings are surprising given the results of a prior investigation that found education (an SES indicator) moderated the relation of arterial stiffening (indexed by cfPWV) to performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Stroop Color Word Reading Test (DuBose, Moser, Harlynn, Fiedorowicz, &

Pierce, 2019) with poorer performance displayed by those with higher cfPWV and lower levels of education. In addition, low educational attainment has been a robust indicator of longitudinal PWV increases (Trudel et al., 2016).

It is difficult to explain why persons of low SES might benefit from higher levels of PWV with respect to select aspects of cognitive performance. One recent theory considers the persistent linkage of low SES with stress to provide a possible explanatory framework. In that regard, individuals of low SES are particularly vulnerable to chronic aversive experiences at least in part as a result of limited resources, lack of access to quality services, and neighborhood characteristics (e.g., disorder). These aversive experiences place those of low SES at risk of experiencing greater acute and chronic stress levels than their higher SES peers. Prior research has indeed reported that individuals who are socioeconomically disadvantaged are more likely to experience stressful life events (Brady & Matthews, 2002). Additionally, socioeconomic disadvantage is correlated with psychophysiological dysregulation, including greater resting blood pressure, higher levels of the stress hormone cortisol (Cohen, Doyle, & Baum, 2006), elevated overnight levels of cortisol and epinephrine, and higher levels of allostatic load (Evans & English, 2002; Schulz, Mentz, Lachance, Johnson, Gaines, & Israel, 2012). A preponderance of prior investigations have demonstrated that high chronic stress levels are associated with lower levels of memory function (Evans & Fuller-Rowell, 2013; Evans & Schamberg, 2009; Jelicic & Bonke, 2001; Mika et al., 2012; Peavy et al., 2009), attention and attentional control (Liston, McEwan, & Casey, 2009), executive functioning (Mika et al., 2012), and volumetric decreases in the hippocampus (McEwen, 2000; Kim, Song, & Kosten, 2005). However, in *contrast* to this work, there is an emerging body of literature noting significant associations

between higher levels of stress (including that associated with living in low SES conditions) and *better* cognitive functioning.

Several authors have argued that because those living in poverty are more likely to inhabit environments that are unpredictable and unstable, these environments may promote an adaption towards present-focused cognitive techniques in which vigilance is heightened, impulsive reactions are encouraged, and more energy is given towards capturing immediate benefits (Frankenhuis, Panchanathan, & Nettle, 2016). Evidence for this phenomenon is suggested by recent findings wherein individuals who were raised in unpredictable conditions related to SES displayed enhanced set shifting abilities – such as efficiently switching between different tasks – a processes that reflects better executive functioning - particularly in an experimental condition of simulated uncertainty (Mittal, Griskevicisu, Simpson, Sung, & Young, 2015). In this novel work, participants reported the level of environmental harshness and unpredictability (family SES) during their childhood. They were then asked to complete cognitive tasks measuring response inhibition (Stroop, stop signal task, anti-saccade task) and set shifting abilities (number – letter task, color – shape task, category switch task) under experimental conditions of uncertainty (induced by having participants read an article about future economic uncertainty) or without uncertainty (control condition). Higher levels of set shifting abilities were found in the experimental group experiencing situational uncertainty. Further, greater unpredictability in one's childhood environment was associated with better performance on set shifting tasks in the uncertainty condition. The authors concluded that the experience of a more unpredictable childhood environment may influence adult cognitive shifting ability dependent on the experience of unpredictability in the environment (akin to living in poverty). These results informed the authors' development of the sensitized specialization

hypothesis that posits cognitive improvements in situations of uncertainty that may act as an ecological adaptation in order to form memories and associations quickly and efficiently (Frankenhuis & Nettle, 2020). Such adaptations may involve altered cognitive processes in the creation of these memories and associations, such as cognitive set shifting and working memory capacity.

It is possible that the results of the above investigation may help explain the present study's findings. In that regard, set shifting is considered a key component of executive functioning (Miyake et al., 2000). Performance of the Verbal Fluency test (see Troyer, Moscovitch, & Winocur, 1997) and the BTA (Schretlen, Bobholz, & Brandt, 1996) both require set shifting abilities. Thus, the higher levels of performance noted on these measures among those living in poverty may be consistent with the sensitized specialization hypotheses. However, that the higher levels of performance among those living in poverty were only found among those with greater PWV requires explanation and could conceivably reflect nonlinear relations of PWV to set shifting with benefit at moderate levels (see E. D. Nilsson et al., 2014). Further, the beneficial relation of poverty status and PWV to BTA performance was only noted among Whites but not African Americans. It is possible that the neurocognitive risks associated with self-identified African American race may have countered any beneficial effects of SES-related stress on cognition.

A challenge to the above interpretation pertaining to the sensitized specialization hypothesis is the fact that set shifting abilities are also assessed by Part B of the Trail Making Test which was not associated with PWV and poverty status in the present investigation (Table 12). However, in contrast to Verbal Fluency and BTA, performance on the Trail Making Test is also heavily dependent on visual tracking ability and perceptuo-motor speed (Strauss et al.,

2006) which may help explain the differential findings. Taken together, it is conceivable that living in (and/or being raised in) an unpredictable environment – a characteristic commonly seen in those with low SES – imparts specific adaptations that facilitate better set shifting abilities which are assessed by both the Verbal Fluency and BTA measures (Schwabe, 2016). Yet, it remains unclear why that relation would be noted solely in the context of higher PWV.

The sensitized specialization hypothesis may also help explain this current study's findings for CVLT Long Delay Recall, a test of verbal memory. One prior investigation has noted a significant relation between stress and better verbal memory performance. Rosnick, Small, McEvoy, Borenstein, and Mortimer (2007) studied the association between negative life events and cognitive performance in multiple domains among a sample of older adults. In this study, analyses involved both an aggregate measure of stress from 24 items on the Louisville Older Persons Events Schedule (LOPES) as well as individual component analysis. The LOPES required participants to indicate which, if any, stressful events had occurred to them in the past 12 months, and to then rate how much of an effect that event had on their lives (1 = no effect, 2 = slight effect, 3 = moderate effect, 4 = strong effect). The researchers found a significant correlation between more negative life events and the recall of more words on a test of verbal memory (Hopkins Verbal Learning Test) and better performance on a response inhibition test (Stroop Test), similar outcomes to the present study's significant findings for and CVLT Long Delay Recall and BTA, respectively. However, these associations did not withstand adjustment for sociodemographic variables. Yet, individual items related to experiencing the injury or illness of a friend were associated with better verbal memory and attention performance even after adjustment for sociodemographic variables.

Although speculative, select biological mechanisms may partially support the sensitized specialization hypothesis. In that regard, multiple studies have demonstrated the negative effects of cortisol – a glucocorticoid synthesized and released by the adrenal gland in response to the detection of perceived threat – on working memory and set-shifting ability (Plessow, Fischer, Kirschbaum, & Goschke, 2011; Schoofs, Wolf, & Smeets 2009; Shield, Bonner, & Moons, 2015). However, these effects have been suggested to be time dependent, with Shields at al. (2015) illustrating genomic (slow acting) *improvements* in working memory performance after an initial phase of impairment following cortisol administration. This may suggest positive effects of stress-induced cortisol response on working memory within select time frames. Similar biological mechanisms have been proposed with respect to enhancement of inhibitory control in the context of stress. In one study, participants who underwent a socially evaluated cold pressor test later showed improvements on a test of inhibitory control (Stop-signal test) compared to controls (Schwabe, Huffken, Tegenthoff, & Wolf, 2013). This effect, however, disappeared when participants were administered a mineralocorticoid receptor (MR) antagonist, suggesting the mediated involvement of these intracellular receptors within the stress-response inhibition association.

In sum, it is challenging to explain why PWV was positively associated with select aspects of cognitive function among those living in poverty in the present investigation. Select available literature, and the associated sensitization specialization hypothesis, offers a potentially relevant perspective on pathways by which SES-related stress could conceivably be involved in the enhancement of set-shifting abilities and verbal memory. Nonetheless, these mechanistic processes, and underlying biological correlates, remain highly speculative. This interpretation

also relies on the supposition that the true relation of PWV to cognitive function in the present sample is nonlinear with moderate levels conferring cognitive benefit.

Present Interactions After Adjustment for Depression and CVD Risk Factors (Aim 2)

The second study aim built upon the first by examining whether any noted significant relations of PWV and cognitive function would be eliminated by adjustment for depressive symptomatology or CVD risk factors. Despite the fact that the few significant findings were in the opposite direction of those expected, we nevertheless explored these models.

Hierarchal entry of depression and CVD risk factors revealed continued significant associations between PWV and both verbal memory (as indexed by the CVLT Long Delay Recall) and divided attention (as indexed by BTA). This finding was expected given that the positive direction of the primary associations was not hypothesized. Nonetheless, prior literature is mixed more generally with respect to whether adjustments for covariates attenuate or render PWV-cognition associations nonsignificant. For example, in several investigations, inverse associations between PWV and cognitive screening tests, as well as composite scores for global cognition, visual-spatial memory, verbal episodic memory, and scanning and tracking have remained significant after covariate adjustments via hierarchal regression (Elias et al., 2009; Zhong et al., 2014). Select covariates examined included known CVD risk factors such as diabetes mellitus, total cholesterol, and cigarette usage (Elias et al., 2009) as well as pulse rate, BMI, cholesterol, HbA1c, smoking and drinking behavior, CVD history, hypertension, physical activity, and depression (Zhong et al., 2014). However, other studies have found an attenuated PWV-cognition association following entry of covariates in hierarchal regression. Kim et al. (2017) reported a diminished relation of PWV to cognitive functioning with adjustments for

cardiovascular risk factors. Additional adjustment for age, sex, race, Charlson comorbidity index, and baseline reading score eliminated the association of PWV and TMT completion times.

In contrast to the above findings, the PWV–Verbal Fluency association was rendered non-significant after hierarchical adjustment for depressive symptomatology. However, subsequent moderated mediation analyses revealed that depressive symptoms did not mediate the interactive relation of PWV and poverty status to Verbal Fluency performance. However, higher CES-D scores were independently and negatively associated with Verbal Fluency performance. Significant negative relations of depressed affect to BTA and CVLT Delayed Recall scores were similarly noted in the hierarchical regression models. These findings are not surprising given the known negative impact of depressive symptoms on cognitive function specifically in the domains of executive function, processing speed, and attention (Hasselbalch et al., 2011), as well attentional shifting abilities (Beats, Sahakian, & Levy, 1996).

In sum, because the direction of the noted associations of PWV and poverty status to cognitive function were directionally opposite to our hypotheses, it is not surprising that these findings were not explained by (or mediated by) depressive symptoms or CVD risk factors. Given the sensitized specialization hypothesis and the possibility of harsh and unpredictable environments being associated with improved cognitive outcomes, it is possible that the relations of PWV and poverty status to CVLT Delayed Recall, BTA, and Verbal Fluency performance may have been rendered nonsignificant with the addition of a psychological stress (or environmental unpredictability) measure or cortisol levels.

Strengths and Limitations

This study had various strengths and limitations that warrant mention. As stated in the literature review, this study further extended the literature by using scores on individual

neurocognitive tests instead of cognitive screening measures. Many studies within the PWV-cognition literature used the MMSE, 3MS, or MoCA as opposed to clinical neuropsychological measures of cognitive performance, which limits specificity of information on the relation between PWV and cognition. A main strength of the present study was use of a more extensive battery in order to clarify these nuanced associations. Additionally, we also utilized raw individual test scores instead of composite scores, further allowing us to better elucidate PWV-cognition relations. This study was also the first to explore health disparities in the PWV-cognition association and to examine the outcomes for traditionally disenfranchised groups. We utilized a racially and socioeconomically diverse non-clinical population, a sample not typical in the available literature (Alvarez-Bueno et al., 2020). In addition, the participants were mostly middle-aged with a similar number of men (44.3%) and women (55.7%), features not commonly seen in the CVD literature. These strengths underscore the generalizability of this study while simultaneously allowing for elucidation of patterns of PWV-cognition relations in understudied samples. This work can provide the foundation for future research in the realm of arterial stiffness and its influence on cognition within a health disparities framework.

This study is not without limitations. One particularly salient potential limitation is the use of stricter exclusion criteria for participants as compared to prior literature. This may have limited the study's generalizability, as well as truncating variability in PWV and cognitive function. In that regard, we excluded participants with a history of stroke, transient ischemic attack, dementia, other neurological disease (e.g., multiple sclerosis), history of cardiac or carotid surgeries, dialysis, and heart failure. Much of the prior literature on PWV and cognition did not exclude individuals with some or most of these medical conditions (Alvarez-Bueno et al., 2020). Another limitation is the relatively low percentage of participants with high PWV readings. The

analysis included only 85 individuals (4.5% of entire sample) with PWV readings above 12 m/s, the cutoff above which PWV poses the greatest risk to downstream tissue integrity (Scuteri & Wang, 2014; Zhong et al., 2014). This sample's mean PWV value was 8.10 m/s, which is well below the mean of other studies that examined community-based samples (Benetos et al., 2014; Cooper et al., 2016; Fukuhara et al., 2006). The limited range may have limited the ability to uncover significant relations between PWV and cognitive function.

Another limitation of the study was its cross-sectional design. A cross-sectional analysis only provides a general snapshot of one point in time for PWV-cognition associations. A longitudinal method, contrastingly, would have provided a better picture of any long-term effect of PWV on cognition and allowed for identification of temporal associations. Also, using a dichotomous proxy of poverty status as a measure of SES limits the ability to capture distinct hardships specifically associated with those living below the 125% federal poverty line. While this variable determines a particular income that is adjusted for household size, it removes nuance that a continuous SES variable would provide. The parent study did not have a continuous income variable, in large part because many participants had difficulty calculating their annual income. Utilizing variables that capture a greater a range of SES may be beneficial for future work.

A larger neuropsychological battery that included more cognitive domains may expand the ability to observe a relation between PWV and cognitive outcomes. The present study may have benefited from additional cognitive tests in the domains of psychomotor movement and dexterity, visuospatial skills, language skills, and processing speed. Given the significant findings with cognitive set shifting, another measure of cognitive flexibility, such as the Wisconsin Card Sorting Test, may have also been helpful. Examination of additional moderating

variables such as age and hypertension status could also be useful. Hypertension is a well-known correlate of arterial stiffness, particularly among African Americans (Arnett et al., 2000; Kuipers et al., 2019; Safar et al., 2018) and is also associated with poorer cognitive performance (Iadecola et al., 2016; Knecht, Wersching, Lohmann, Berger, and Ringlestein, 2009). Furthermore, age is a major determinant of central arterial stiffening, with the prevalence of stiffening increasing with age (Benetos et al., 2002). Examining these variables as moderators may uncover valuable components of PWV-cognition associations.

Implications and Future Directions

Despite the largely null findings of the present study, there were several significant associations of PWV, poverty status, and race on cognition within the domains of verbal memory, attention, and executive function. While these findings largely contradict the literature, they may suggest adaptive cognitive abilities employed by those living in poverty (Frankenhuis, Panchanathan, & Nettle, 2016; Frankenhuis & Nettle, 2020; Leonard et al., 2015). It is further conceivable that such environmental adaptation would promote better acute utilization (or increased activity) of the genomic effects of glucocorticoids within brain systems known to be involved in processing of working memory and executive functioning. This could result in improved cognitive set shifting abilities and memory function and allow individuals to more quickly orient towards perceived threats within their volatile environment.

These findings may also suggest the possibility of nonlinear associations of PWV and cognition given that the sample was younger and had a largely normal range of PWV readings in contrast to prior investigations. PWV increases with age and may not begin to negatively impact cognition until after the age of 50 years (Al Hazzouri et al., 2013). In addition, nonlinear associations may only be noted in samples with a broader range of PWV that includes clinically

elevated values. This study further contributes to the PWV-cognition literature by probing moderators rarely included in other studies of subclinical vascular disease and cognitive function. While these findings were largely non-significant, there remains the possibility that race and/or SES moderates PWV-cognition relations in ways that this study was unable to determine.

Regardless of these results, this project serves as an important reminder for the continued study of health disparities and inclusion of traditionally marginalized populations in epidemiological research. Doing so enables researchers to characterize any associated group differences and can serve as a foundation for important public policy initiatives. Results presented above further allow for a reconceptualization of cognitive risks and benefits associated with low SES and may serve to counter the associated negative stigma surrounding these individuals.

Future research could contrast findings associated with composite test scores versus individual test scores. Additionally, a longitudinal study examining both the current and additional sociodemographic trajectories of PWV-cognition relations would be a valuable endeavor for future work. Examples of such additional moderators include age, hypertension status, other SES indicators, or other psychosocial measures (such as stress) which may help to build upon the present study. Lastly, evaluation of nonlinear associations of PWV to cognitive function would be useful.

Conclusion

Largely inconsistent with the proposed hypotheses and with prior literature, the present investigation did not find significant interactive relations of PWV, race, and poverty status, or independent relations of PWV, for the majority of cognitive outcomes measures. Furthermore,

although several significant associations were noted, results were directionally opposite those posited in that Whites living in poverty displayed greater performance on BTA and higher levels of CVLT Delayed Recall and Verbal Fluency performance were noted among those living in poverty who had higher PWV. These results suggest that those living in poverty may display particular resiliency strategies that better allow them to adapt and thrive in unpredictable and volatile environments. However, that such resiliency was only found among those with higher PWV may suggest some benefit to mid-range, non-clinical levels of PWV and the possible presence of non-linear associations of PWV and cognitive outcomes.

This study was the first, to my knowledge, to examine the interactive relations of PWV, poverty status, and race on cognition function. The work may inform future research examining both similar and different SES proxies or alternate moderators. Future work should build upon the present investigation by using additional indicators of SES. Should similar findings be found in which higher levels of cognitive function are noted among those living in poverty, future work should examine the neurobiological correlates of such resilience and seek to amplify and isolate related adaptive strategies. Lastly, these findings emphasize the need to further study the relations of PWV and other forms of subclinical vascular disease to cognitive function in racially and socioeconomically diverse populations across the life span.

Appendices: Table

Table 1.

Study Sample Descriptive Characteristics

Variable	*Mean*	*SD*	*Percent*	*Range*
Age (years)	48.82	9.17	-	30 – 64
% female	-	-	56	-
% African American	-	-	55	-
% Above 125% Federal Poverty Level	-	-	60	-
% Hypertension Diagnosis	-	-	48	-
% Hypertension Prescription	-	-	32	-
% Alcohol Usage	-	-	92	-
% Cigarette Usage	-	-	79	-
% Diabetes Diagnosis	-	-	15	-
% History of Cardiovascular Disease	-	-	4	-
Body Mass Index (kg/m^2)	30.05	7.71	-	14.36 – 62.46
Pulse Wave Velocity (m/s)	8.10	2.49	-	1.82-20.89
Mean Arterial Pressure (mmHg)	88.57	11.63	-	6.67-130.67
Heart Rate (bpm)	67.19	13.00	-	35 – 121
Depression Symptomatology (CES-D Score)	15.30	11.24	-	0 – 55
Neuropsychological Outcomes				
Digit Span Forwards	7.19	2.20		1 - 14
Digit Span Backward	5.61	2.21		0 - 14
BVRT Total Errors	6.69	5.26		0 - 30
CVLT List A Total	24.19	6.62		5 - 44
CVLT Short Recall	7.03	3.04		0 - 16
CVLT Delayed Recall	7.14	3.03		0 - 16
Brief Test of Attention	6.58	2.21		0 - 10
Trail Making Test A (sec.)	38.82	43.26		13 - 600
Trail Making Test B (sec.)	159.28	169.16		25 - 600
Verbal Fluency	18.61	5.35		3 - 40

Note: Percentage alcohol and percentage cigarette usage were dichotomized into former & current usage versus never used.

Table 2.

Correlation Coefficient Matrix of Predictors and Moderators from Backwards Elimination (Aim 1)

Variable	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
(1) PWV	-										
(2) Race	.055*	-									
(3) Poverty	-.052*	.118**	-								
(4) Age	.344**	-.009	-.051*	-							
(5) Sex	.002	.009	-.032	-.006	-						
(6) Education	-.079**	-.020	-.238**	-.004	-.013	-					
(7) Alcohol	.007	-.035	-.066**	.006	.130**	-.039	-				
(8) Cigarette	.040	.029	.048*	.079**	.101**	-.196**	.186**	-			
(9) MAP	.250**	.067**	.035	.191**	.085**	-.072**	-.031	-.019	-		
(10) HR	.182**	-.032	.043	.051*	-.073**	-.052*	-.030	-.013	.090**	-	
(11) Hyper. Meds.	.205**	.083**	-.007	.355**	-.049*	.002	-.026	-.007	.173**	.123**	-

*$p < .05$; **$p < .01$. Note: Alcohol = alcohol usage dichotomized into "ever/never used," Cigarette = cigarette usage dichotomized into "ever/never used," HR = Heart rate, Hyper. Meds. = Antihypertensive medication usage

Table 3.

Correlation Coefficient Matrix of Predictors, Moderators, Outcomes, and Select Covariate Variables

Variable	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
(1) Age	-																
(2) Sex	-.006	-															
(3) Race	-.009	.009	-														
(4) Poverty	-.051*	-.032	.118**	-													
(5) PWV	.344**	.002	.055*	-.052*	-												
(6) DSF	-.08**	.033	-.151**	-.133**	-.035	-											
(7) DSB	-.101**	-.019	-.238**	-.153**	-.048*	.566**	-										
(8) BVRT	.210**	-.093**	.064**	.096**	.129**	-.259**	-.341**	-									
(9) CVLT T	-.185**	-.187**	-.167**	-.115**	-.061*	.272**	.335**	-.342**	-								
(10) CVLT S	-.23**	-.152**	-.198**	-.099**	-.052*	.213**	.315**	-.3**	.773**	-							
(11) CVLT L	-.22**	-.169**	-.21**	-.094**	-.05*	.216**	.303**	-.311**	.791**	.866**	-						
(12) BTA	-.096**	-.062*	-.195**	-.152**	-.061*	.299**	.414**	-.295**	.293**	.248**	.282**	-					
(13) Trails A	.285**	.111**	.192**	.127**	.109**	-.224**	-.256**	.313**	-.279**	-.271**	-.291**	-.332**	-				
(14) Trails B	.236**	.059*	.264**	.169**	.099**	-.344**	-.451**	.448**	-.433**	-.389**	-.401**	-.422**	.513**	-			
(15) Fluency	-.126**	.059*	-.151**	-.144**	-.041	.216**	.297**	-.31**	.349**	.335**	.324**	.203**	-.279**	-.346**	-		
(16) BMI	.038	-.227**	.021	-.056*	.228**	-.038	.007	.039	.106**	.102**	.137**	-.04	.01	.016	.037	-	
(17) CES	-.057	-.102**	-.041	.148**	-.006	-.130**	-.118**	-.189**	-.184**	-.142**	-.151**	-.121**	.080**	.151**	-.134**	.014	-

*$p < .05$; **$p < .01$. Note: BVRT = BVRT Total Errors; CVLT T = CVLT List A Total Score, CVLT S = CVLT Short Delayed Recall Score, CVLT L = CVLT Long Delayed Recall Score; CES = Center for Epidemiological Studies – Depression Scale; Trails A and B log transformed; Pearson's point-biserial correlations used for associations between continuous and dichotomous variables, Phi correlation coefficient used for associations between two dichotomous variables.

Table 4.

Unstandardized Coefficients from Backwards Elimination Models of Hierarchal Regression Analyses for Digit Span Forwards (Aim 1)

	Model 1	Model 2	Model 3
Age	-.022**	-.022**	-.021**
Sex	.052	.053	.058
Education	.189**	.180**	.189**
Alcohol Use	.363	.362	.359
Cigarette Use	.344*	.344*	.339*
MAP	-.004	-.004	-.003
HR	-.003	-.003	-.003
Hypertensive Medication	.025	.025	.033
PWV	-.007	-.001	.015
Race	-.726	-.610	-.631**
Poverty Status	-1.136	-.853*	-.297**
PWV × Race	.011	-.003	-
PWV × Pov Stat	.101	.066	-
Race × Pov Stat	.481	.037	-
PWV × Race × Pov Stat	-.055	-	-

*$p < .05$; **$p < .01$. Note: Model 1 is Step 1 (see methods). Model 2 is elimination of three-way interaction. Model 3 is elimination of two-way interactions.

Table 5.

Unstandardized Coefficients from Backwards Elimination Models of Hierarchal Regression Analyses for Digit Span Backwards (Aim 1)

	Model 1	Model 2	Model 3
Age	-.026**	-.025**	-.025**
Sex	-.105	-.105	-.101
Education	.209**	.209**	.208**
Alcohol Use	.169	.168	.163
Cigarette Use	.330*	.330*	.332*
MAP	-.002	-.002	-.002
HR	-.001	-.001	-.001
Hypertensive Medication	.001	.001	.001
PWV	.016	.019	.013
Race	-.913*	-.857*	-1.004**
Poverty Status	-.694	-.557	-.325**
PWV × Race	-.015	-.022	-
PWV × Pov Stat	.039	.022	-
Race × Pov Stat	.301	.087	-
PWV × Race × Pov Stat	-.027	-	-

*$p < .05$; **$p < .01$. Note: Model 1 is Step 1 (see methods). Model 2 is elimination of three-way interaction. Model 3 is elimination of two-way interactions.

Table 6.

Unstandardized Coefficients from Backwards Elimination Models of Hierarchal Regression Analyses for BVRT Total Errors (Aim 1)

	Model 1	Model 2	Model 3
Age	.122**	.121**	.121**
Sex	-.969**	-.972**	-1.002**
Education	-.458**	-.457**	-.459**
Alcohol Use	-1.341**	-1.338**	-1.320**
Cigarette Use	-.100	-.098	-.101
MAP	.005	.005	.005
HR	.013	.013	.013
Hypertensive Medication	-.379	-.376	-.377
PWV	.068	-.043	.089
Race	.637	.167	.593*
Poverty Status	3.108*	1.966*	.465
PWV × Race	.057	.114	-
PWV × Pov Stat	-.219	-.076	-
Race × Pov Stat	-3.185	-1.390**	-
PWV × Race × Pov Stat	.223	-	-

*$p < .05$; **$p < .01$. Note: Model 1 is Step 1 (see methods). Model 2 is elimination of three-way interaction. Model 3 is elimination of two-way interaction

Table 7.

Unstandardized Coefficients from Backwards Elimination Models of Hierarchal Regression Analyses for CVLT Part A Total Recall (Aim 1)

	Model 1	Model 2	Model 3
Age	-.159**	-.159**	-.155**
Sex	-2.608**	-2.606**	-2.571**
Education	.711**	.709**	.709**
Alcohol Use	1.485*	1.480*	1.470*
Cigarette Use	.492	.490	.470
MAP	-.005	-.006	-.004
HR	.014	.015	.016
Hypertensive Medication	.498	.494	.515
PWV	-.003	.028	.064
Race	-2.629*	-2.080	-2.179**
Poverty Status	-4.934*	-3.554**	-.756*
PWV × Race	.012	-.053	-
PWV × Pov Stat	.436	.266	-
Race × Pov Stat	3.106	.988	-
PWV × Race × Pov Stat	-.261	-	-

*$p < .05$; **$p < .01$. Note: Model 1 is Step 1 (see methods). Model 2 is elimination of three-way interaction. Model 3 is elimination of two-way interactions.

Table 8.

Unstandardized Coefficients from Backwards Elimination Models of Hierarchal Regression Analyses for CVLT Short Delay Recall (Aim 1)

	Model 1	Model 2	Model 3
Age	-.093**	-.093**	-.092**
Sex	-.923**	-.922**	-.911**
Education	.270**	.269**	.269**
Alcohol Use	.484	.479	.467
Cigarette Use	.201	.199	.203
MAP	.000	-.001	.000
HR	.007	.007	.007
Hypertensive Medication	.155	.155	.152
PWV	.053	.067	.050
Race	-1.170	-.910	-1.205**
Poverty Status	-1.422	-.765	-.317*
PWV × Race	-.016	-.047	-
PWV × Pov Stat	.116	.034	-
Race × Pov Stat	1.258	.252	-
PWV × Race × Pov Stat	-.124	-	-

*$p < .05$; **$p < .01$. Note: Model 1 is Step 1 (see methods). Model 2 is elimination of three-way interaction. Model 3 is elimination of two-way interactions.

Table 9.

Unstandardized Coefficients from Backwards Elimination Models of Hierarchal Regression Analyses for CVLT Long Delay Recall (Aim 1)

	Model 1	Model 2
Age	-.088**	-.087**
Sex	-1.019**	-1.012**
Education	.266**	.265**
Alcohol Use	.370	.372
Cigarette Use	.155	.151
MAP	-.002	-.002
HR	.011	.011*
Hypertensive Medication	.131	.134
PWV	-.012	.015
Race	-1.955**	-1.274**
Poverty Status	-2.764**	-1.414**
PWV × Race	.062	.010
PWV × Pov Stat	.272*	.140*
Race × Pov Stat	2.115	.322
PWV × Race × Pov Stat	-.206	-

*$p < .05$; **$p < .01$. Note: Model 1 is Step 1 (see methods). Model 2 is elimination of three-way interaction.

Table 10.

Unstandardized Coefficients from Backwards Elimination Models of Hierarchal Regression Analyses for BTA (Aim 1)

	Model 1
Age	-.021**
Sex	-.354**
Education	.138**
Alcohol Use	.733**
Cigarette Use	.063
MAP	-.001
HR	-.012**
Hypertensive Medication	-.096
PWV	-.024
Race	-.898*
Poverty Status	-3.112**
PWV × Race	.001
PWV × Pov Stat	.330**
Race × Pov Stat	2.664**
PWV × Race × Pov Stat	-.315**

*$p < .05$; **$p < .01$. Note: Model 1 is Step 1 (see methods).

Table 11.

Unstandardized Coefficients from Backwards Elimination Models of Hierarchal Regression Analyses for TMTA (Aim 1)

	Model 1	Model 2	Model 3
Age	.006**	.006**	.006**
Sex	.045**	.045**	.045**
Education	-.011**	-.011**	-.011**
Alcohol Use	-.046**	-.046**	-.046**
Cigarette Use	-.004	-.004	-.004
MAP	.000	.000	.000
HR	.000	.000	.000
Hypertensive Medication	.001	.001	.001
PWV	-.002	-.001	.000
Race	.036	.061	.068**
Poverty Status	-.004	.059	.035**
PWV × Race	.005	.002	-
PWV × Pov Stat	.006	-.002	-
Race × Pov Stat	.081	-.016	-
PWV × Race × Pov Stat	-.012	-	-

*$p < .05$; **$p < .01$. Note: Model 1 is Step 1 (see methods). Model 2 is elimination of three-way interaction. Model 3 is elimination of two-way interactions.

Table 12.

Unstandardized Coefficients from Backwards Elimination Models of Hierarchal Regression Analyses for TMTB (Aim 1)

	Model 1	Model 2	Model 3
Age	.009**	.009**	.009**
Sex	.034*	.034*	.033*
Education	-.033**	-.033**	-.033**
Alcohol Use	-.066*	-.066*	-.065*
Cigarette Use	-.009	-.009	-.010
MAP	.000	.000	.000
HR	.001*	.001*	.001*
Hypertensive Medication	.005	.005	.005
PWV	-.006	-.007	-.004
Race	.150*	.129*	.170**
Poverty Status	.146	.094	.061**
PWV × Race	.004	.006	-
PWV × Pov Stat	-.008	-.002	-
Race × Pov Stat	-.109	-.028	-
PWV × Race × Pov Stat	.010	-	-

*$p < .05$; **$p < .01$. Note: Model 1 is Step 1 (see methods). Model 2 is elimination of three-way interaction. Model 3 is elimination of two-way interactions.

Table 13.

Unstandardized Coefficients from Backwards Elimination Models of Hierarchal Regression Analyses for Verbal Fluency (Aim 1)

	Model 1	Model 2
Age	-.080**	-.080**
Sex	.684**	.685**
Education	.538**	.535**
Alcohol Use	1.167*	1.166*
Cigarette Use	.237	.236
MAP	-.011	-.011
HR	-.006	-.006
Hypertensive Medication	.258	.255
PWV	-.063	-.047
Race	-3.380**	-3.099**
Poverty Status	-3.852*	-3.165**
PWV × Race	.159	.125
PWV × Pov Stat	.270	.219*
Race × Pov Stat	2.520	1.438**
PWV × Race × Pov Stat	-.134	-

*$p < .05$; **$p < .01$. Note: Model 1 is Step 1 (see methods). Model 2 is elimination of three-way interaction.

Table 14.

Unstandardized Coefficients from Hierarchal Model Analyses for CVLT Delayed Recall (Aim 2)

	Step 1	Step 2	Step 3
Age	-.087**	-.092**	-.088**
Sex	-1.012**	-1.105**	-.974**
Education	.265**	.229**	.228**
Alcohol Use	.372*	.363	.410
Cigarette Use	.151	.175	.210
MAP	-.002	-.002	-.006
HR	.011*	.013*	.011
Hypertensive Medication	.134	.172	.081
PWV	.015	.011	-.003
Race	-1.274**	-1.329**	-1.291**
Poverty Status	-1.414**	-1.416**	-1.333*
PWV × Pov Stat	.140*	.150*	.145*
CES		-.044**	-.043**
BMI			.035**
Diabetes			-.108
Cholesterol			.001
CVD History			.198

*$p < .05$; **$p < .01$. Note: Step 1 is retained model from hypothesis 1 with significant interaction (see methods). Interaction terms not of interest omitted from table.

Table 15.

Unstandardized Coefficients from Hierarchal Model Analyses for BTA (Aim 2)

	Step 1	Step 2	Step 3
Age	-.021**	-.023**	-.025**
Sex	-.354**	-.395**	-.431**
Education	.138**	.123**	.124**
Alcohol Use	.733**	.733**	.709**
Cigarette Use	.063	.078	.061
MAP	-.001	-.002	-.002
HR	-.012**	-.011*	-.009*
Hypertensive Medication	-.096	-.078	-.010
PWV	-.024	-.021	-.012
Race	-.898*	-.832	-.821
Poverty Status	-3.112**	-3.012**	-3.064**
PWV × Race	.001	-.007	-.007
PWV × Pov Stat	.330**	.327**	.335**
Race × Pov Stat	2.664**	2.521**	2.463**
PWV × Race × Pov Stat	-.315**	-.304**	-.301**
CES		-.019**	-.019**
BMI			-.010
Diabetes			-.322
Cholesterol			.001
CVD History			.238

*$p < .05$; **$p < .01$. Note: Step 1 is retained model from hypothesis 1 with significant interaction (see methods).

Table 16.

Unstandardized Coefficients from Hierarchal Model Analyses for Verbal Fluency (Aim 2)

	Step 1	Step 2
Age	-.080**	-.067**
Sex	.685**	.781**
Education	.535**	.517**
Alcohol Use	1.166*	1.235**
Cigarette Use	.236	.259
MAP	-.011	-.017
HR	-.006	-.009
Hypertensive Medication	.255	.236
PWV	-.047	-.038
Race	-3.099**	-1.557**
Poverty Status	-3.165**	-2.366*
PWV × Pov Stat	.219*	.340
CES		-.036**

*$p < .05$; **$p < .01$. Note: Step 1 is retained model from hypothesis 1 with significant interaction (see methods). Interaction terms not of interest omitted from table.

Appendices: Figures

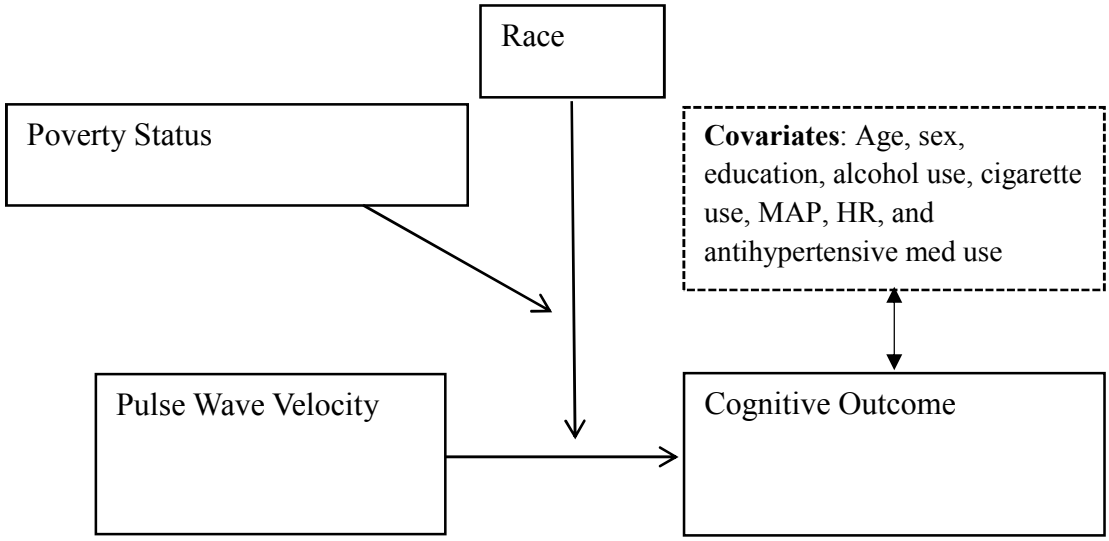

Figure 1. Conceptual Diagram of Moderation Model for Aim 1, Step 1 Base Model

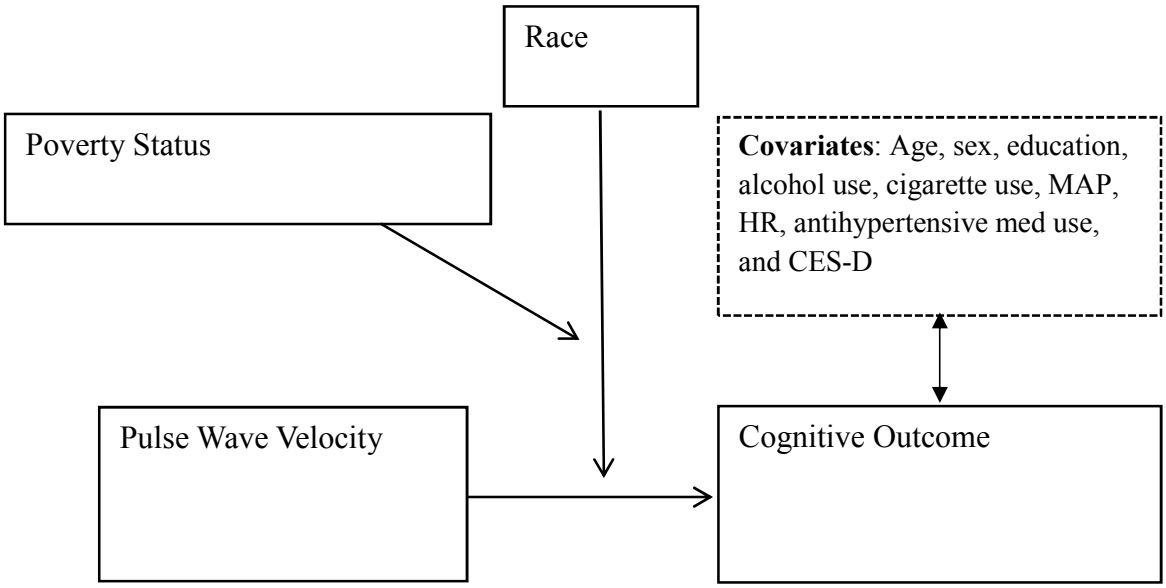

Figure 2. Conceptual Diagram of Moderation Model for Aim 2, Step 2

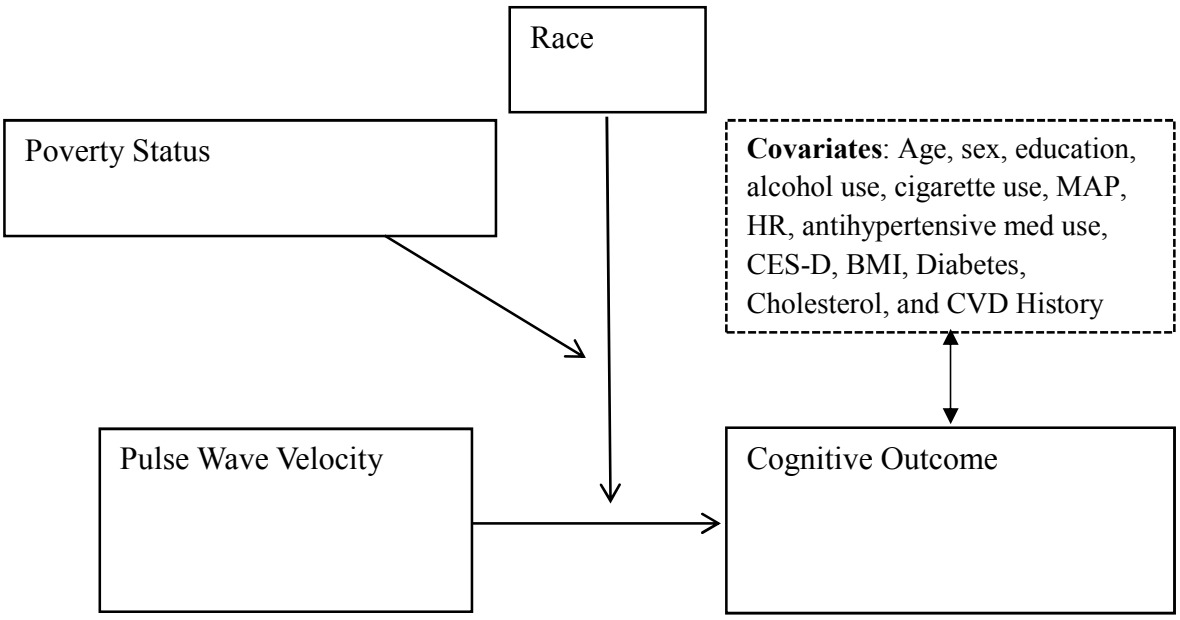

Figure 3. Conceptual Diagram of Moderation Model for Aim 2, Step 3

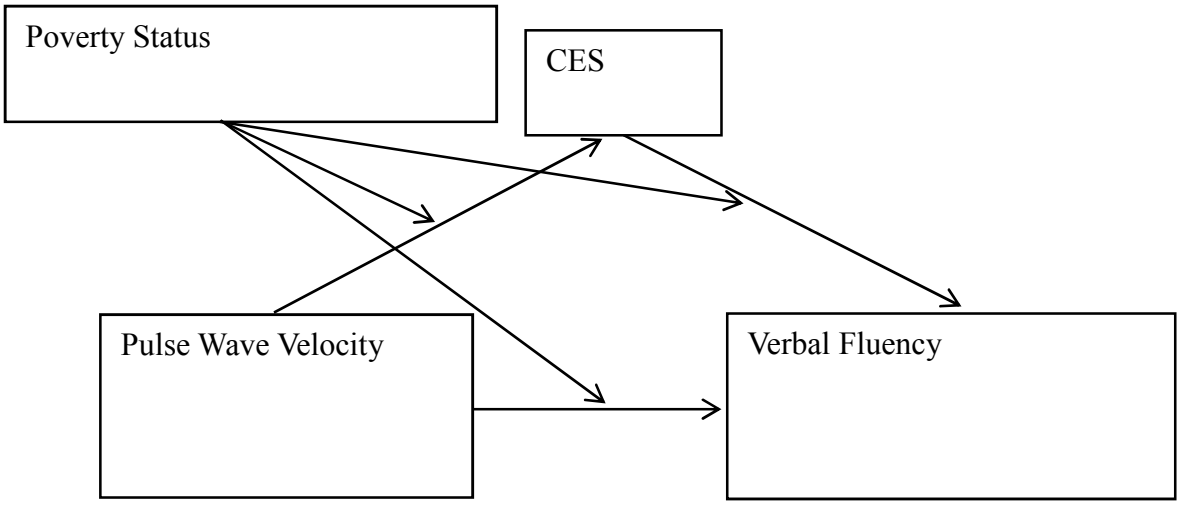

Figure 4. Conceptual Diagram of Moderated Mediation Model for Verbal Fluency

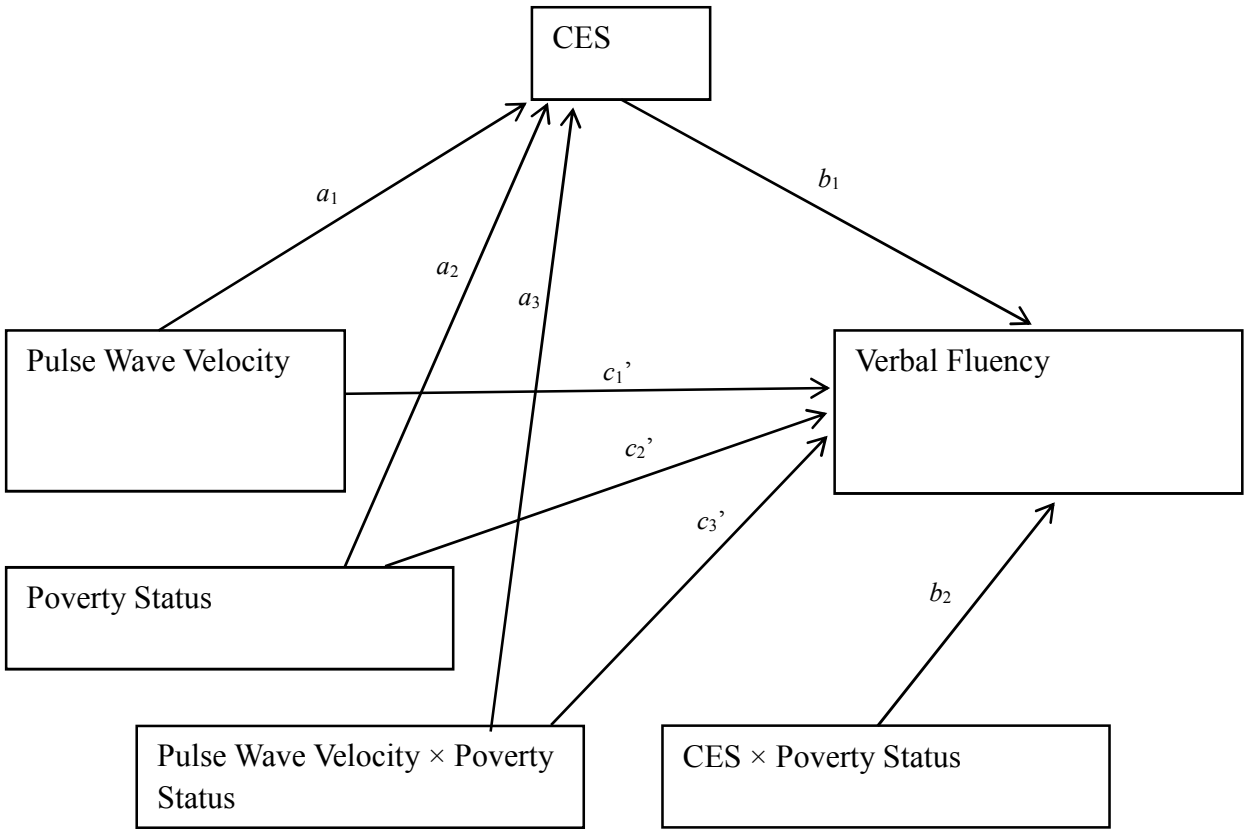

Figure 5. Statistical Path Diagram of Moderated Mediation Model for Verbal Fluency

PWV Predicting CVLT Long Delay Score

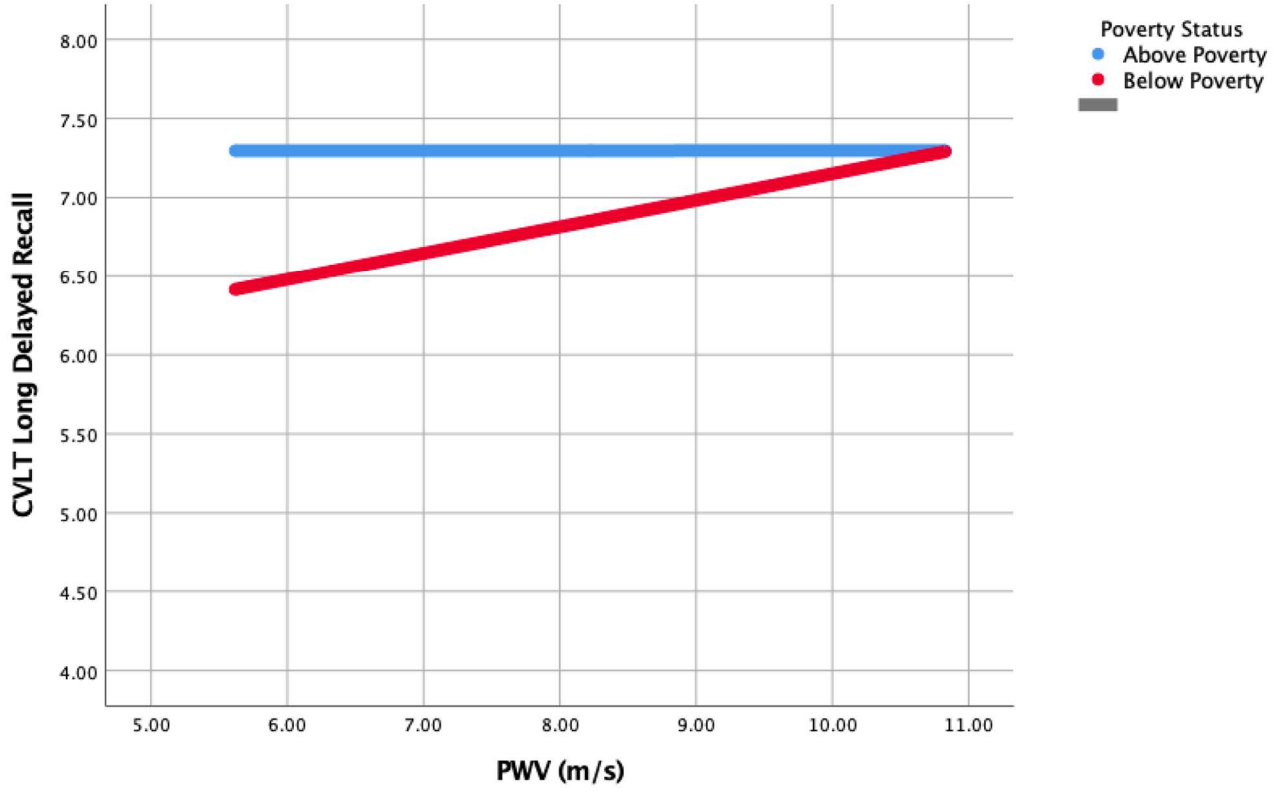

Figure 6. PWV was significantly associated with CVLT Long Delay Score by Poverty Status, such that greater PWV was associated with increased CVLT Long Delay Score among those living in poverty.

PWV Predicting BTA Score

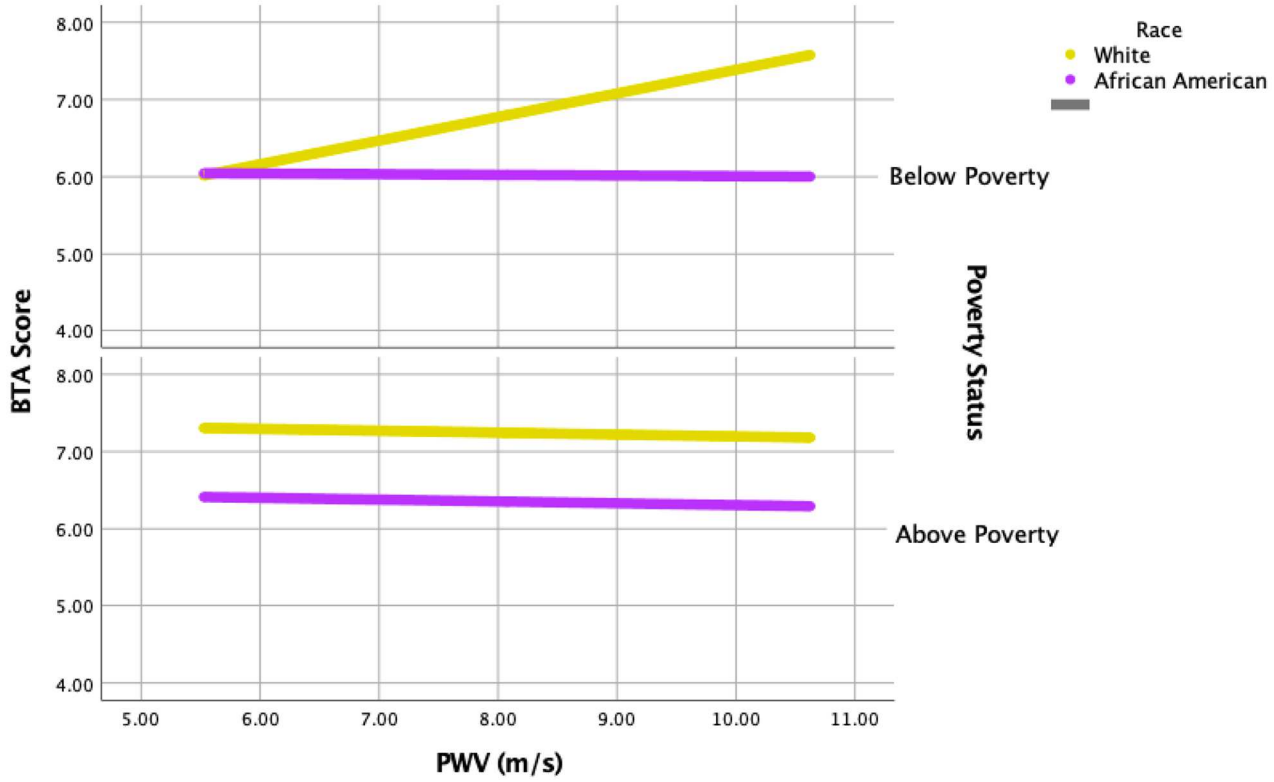

Figure 7. PWV was significantly associated with BTA Score by Poverty Status and Race, such that among Whites living in Poverty, increasing PWV was associated with increased BTA scores

PWV Predicting Verbal Fluency Score

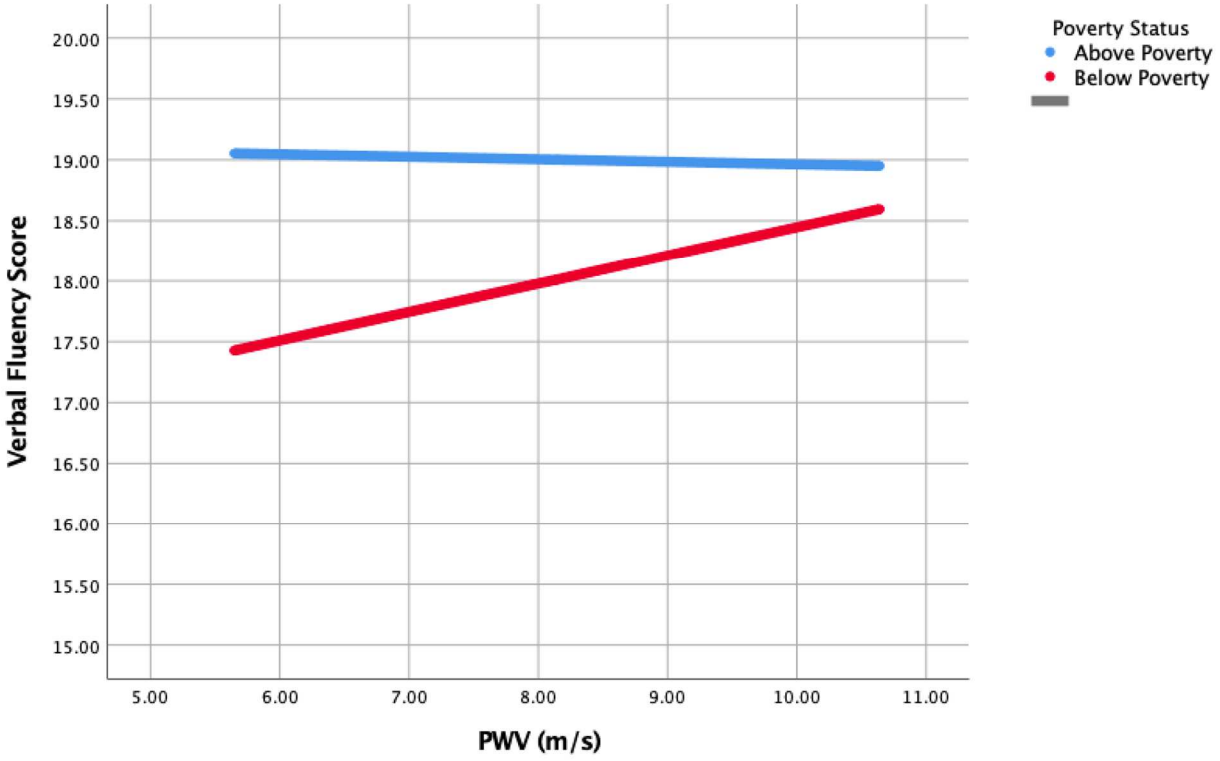

Figure 8. PWV was significantly associated with Verbal Fluency Score by Poverty Status, such that increasing PWV was associated with increased Verbal Fluency among those living in poverty.

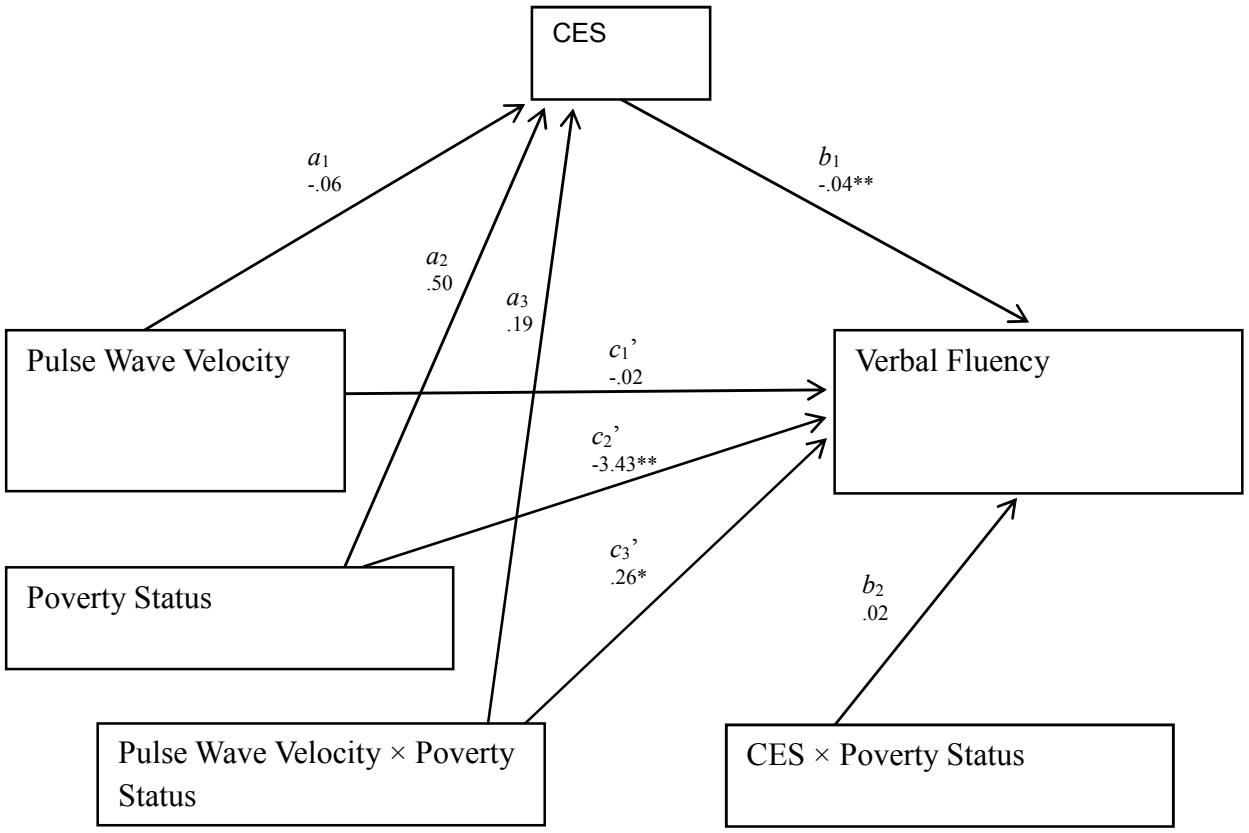

Figure 9. Moderated mediation model for CES mediating the relationship between PWV and Verbal Fluency.

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