MODIFIABLE CARDIOVASCULAR RISK AND COGNITIVE FUNCTION: FINDINGS FROM THE MAINE SYRACUSE LONGITUDINAL STUDY

by

Rachael Valentine Torres

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Applied Physiology

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
AR	Abstract Reasoning
ApoE	Apolipoprotein E
BMI	Body mass index
BP	Blood pressure
CKD	Chronic kidney disease
CRP	C-reactive protein
CVD	Cardiovascular disease
CV	Cardiovascular
CVRFS	Cardiovascular Risk Factor Scale
eGFR	Estimated glomerular filtration rate
FRS	Framingham Risk Score
GMS	General Mental State
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
MCI	Mild cognitive impairment
MSLS	Maine Syracuse Longitudinal Study
PWV	Pulse wave velocity
RF	Risk factor

SD	Standard deviation
ST	Scanning and Tracking
TC	Total cholesterol
tHcy	Total plasma homocysteine
VaD	Vascular dementia
VC	Verbal Comprehension
VEM	Verbal Episodic Memory
VSOM	Visual-Spatial Organization/Memory
WM	Working Memory

ABSTRACT

Complex cognitive changes accompany aging and it will become increasingly important to understand them as the number of adults over 65 years of age increases from 617M in 2015 to 1.6B in 2050. Normative cognitive aging is characterized by subtle cognitive decline, while nonnormative cognitive aging is characterized by accelerated decline resulting in severe disability. The hallmark of nonnormative cognitive aging is dementia, a terminal syndrome that affects 47M people globally and costs >$1T per year. Cognitive decline begins up to 30 years before the emergence of clinical symptoms in the trajectory and an intervention slowing decline could prevent up to 57% of the 131M dementia cases expected by 2050. Cardiovascular disease (CVD) is strongly implicated in dementia pathophysiology and modifiable cardiovascular (CV) risk is a prime target for interventions designed to slow nonnormative cognitive aging and ultimately reduce dementia burden. However, further research characterizing associations between modifiable CV risk and cognitive function is needed before interventions can be developed and implemented.

Multivariable screening tools are used to determine aggregate CV risk and guide treatment decisions in primary care settings. Aim 1 of this research was to determine whether these screening tools could also be used to identify adults early in the nonnormative cognitive aging trajectory when intervention would be most effective. We found that higher Framingham Risk Score (FRS) and Maine Syracuse Longitudinal Study Cardiovascular Risk Factor Scale (MSLS-CVRFS) score predicted lower cognitive function

cross-sectionally, prospectively and longitudinally in 600 community-dwelling adults of the MSLS (M_{Age} 62.0±11.9 years; 61% female).

Modifiable CV risk factors (CV-RFs) are strictly controlled in primary care settings to prevent CVD, albeit their association with cognitive function is less clear. Aim 2 was to determine which major modifiable CV-RFs to target in interventions designed to slow cognitive decline. We found that higher systolic blood pressure (BP), diastolic BP and fasting glucose and lower high density lipoprotein cholesterol (HDL-C) were associated with lower cognitive function cross-sectionally, prospectively and longitudinally in 600 community-dwelling adults of the MSLS (M_{Age} 62.0±11.9 years; 61% female). Associations for systolic BP, diastolic BP and fasting glucose became significant with advancing age, while those for HDL-C were observed at all ages.

CVD and dementia pathophysiology involve arterial stiffening, a process driven by increased modifiable CV and genetic risk. Therapeutic strategies have been proposed to modulate stiffening processes and could be used to slow decline in susceptible adults. However, the underlying cause of decline must be addressed and the role of arterial stiffness in associations between modifiable CV risk and cognitive function is unclear. Aim 3 was to examine arterial stiffness as a mediator of associations between modifiable CV risk and cognitive function in 577 community-dwelling adults of the MSLS (M_{Age} 66.3±11.8 years; 61% female) with variable genetic risk. We found that arterial stiffness mediated cross-sectional associations between modifiable CV risk and cognitive function in carriers, but not noncarriers of the apolipoprotein E (ApoE) ε4 allele.

Our findings have the potential to inform methods for identifying and treating adults early in the nonnormative cognitive aging trajectory. Systolic BP, diastolic BP, fasting glucose, HDL-C and arterial stiffness are important intervention targets that

should be treated early, especially in the context of higher aggregate CV and genetic risk. As interventions are developed, physicians are encouraged to educate patients on the importance of maintaining CV health for promoting enhanced brain aging.

Chapter 1

INTRODUCTION

1.1 Cognitive Aging

The number of adults over 65 years of age worldwide is projected to increase from 617M in 2015 to 1.6B in 2050. (He, Goodkind, & Kowal, 2016) Complex cognitive changes accompany aging and it will become increasingly important to understand them as this population segment grows. Lifespan developmental studies have historically focused on normative cognitive aging, in which cognitive abilities improve throughout early life, remain stable at midlife and decline in late life. (Steinerman, Hall, & Sliwinski, 2010) However, few people remain healthy throughout adulthood and these studies do not adequately consider the effect of disease processes on cognition. Disease-oriented studies have historically focused on nonnormative cognitive aging, in which pathophysiology present in some adults accelerates cognitive decline and causes severe deficits in late adulthood. (Steinerman, Hall, & Sliwinski, 2010) These studies are vital for identifying at risk adults and potential intervention targets, although further work is needed to adequately account for age and related cognitive changes.

1.1.1 Normative Cognitive Aging

Many theories regarding the structure of cognition have been proposed. Spearman (1904) and Spearman and Jones (1950) have provided evidence for a global human ability (g) and a subset of specific abilities correlated with g. More recent theories recognize a complex hierarchy of primary mental abilities known as cognitive domains and

the specific abilities that index them. (McGrew, 2005; Thurstone, 1973) Cognitively healthy adults that exhibit higher global performance tend to have greater function in specific cognitive domains. (Elias, Torres, & Davey, 2018) However, each aspect of cognition is differentially affected by normative aging processes. Commonly examined cognitive domains and changes associated with aging are presented in Table 1.1. Most cognitive domains decline steadily with advancing age from midlife (see Figure 1.1), although deficits observed are minor and do not generally interfere with activities of daily living. (Harada, Love, & Triebel, 2013)

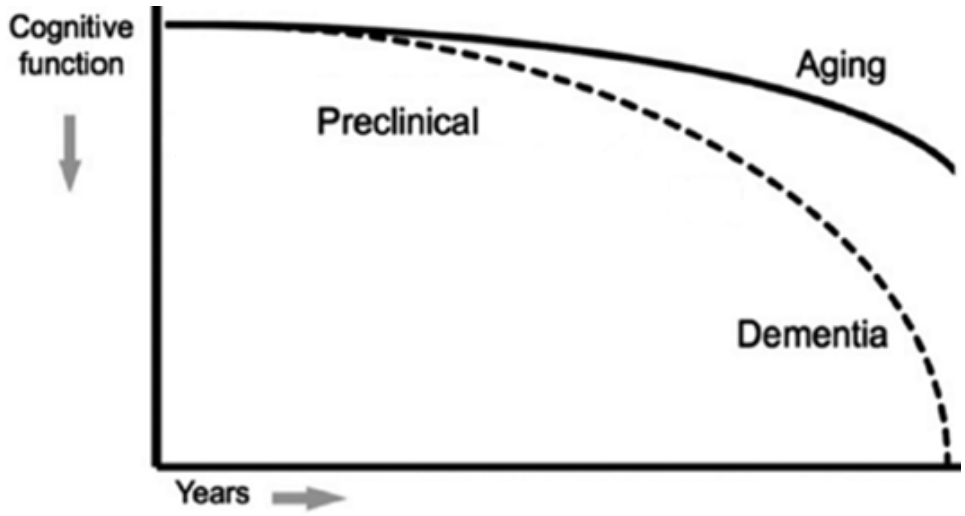

Figure 1.1. Cognitive decline trajectories indicative of normative aging and dementia. Modified from Sperling et al. (2011).

Table 1.1. Commonly examined cognitive domains and changes associated with normative aging.

Cognitive domain	Definition	Normative age-related changes
Attention	The ability to selectively concentrate on relevant information while ignoring irrelevant information. Abilities include: selective, alternating and divided attention.	Attention and its abilities decline steadily throughout adulthood. (Harada, Love, & Triebel, 2013; Glisky, 2007)
Executive Function	A set of mental processes that allow individuals to engage in independent and purposive behavior. Abilities include: planning, reasoning, organization and mental flexibility.	Executive Function declines steadily throughout adulthood. (Dore, Elias, Robbins, Elias, & Brennan, 2007) Executive abilities differ, with reasoning remaining stable. (Harada, Love, & Triebel, 2013)
Language	The ability to produce and comprehend language. Abilities include: object naming, fluency, grammar and syntax.	Language and its abilities remain stable or improve throughout adulthood. (Singh-Manoux, et al., 2012)
Long-Term Memory	The ability to retrieve information no longer being maintained in an active state. Abilities included: episodic, autobiographical and prospective memory.	Long-Term Memory declines steadily throughout adulthood. (Harada, Love, & Triebel, 2013) Memory abilities differ, with episodic memory declining the most. (Glisky, 2007)
Perception	A set of processes that allow individuals to acquire information and make predictions. Abilities included: visual, spatial and auditory perception.	Perception and its abilities decline steadily throughout late life. (Glisky, 2007) Could be the result of vision and hearing loss (Schneider & Pichora-Fuller, 2000).
Processing Speed	The speed with which cognitive abilities are performed and motor responses are achieved. Important for the function of many higher-order cognitive domains.	Processing Speed declines steadily throughout adulthood. (Hoogendam, Hofman, van der Geest, van der Lugt, & Ikram, 2014)
Working Memory	The ability to hold information in memory and manipulate it to complete a task. Important for reasoning and decision-making.	Working Memory declines steadily throughout late life. (Glisky, 2007) Could be the result of Attention (Craik & Byrd, 1982) and Processing Speed (Salthouse, 1995) deficits.

1.1.2 Nonnormative Cognitive Aging

Dementia is the hallmark of nonnormative cognitive aging and is widely regarded as the greatest health and social care challenge of the 21st century. (Alzheimer's Association, 2017) Over 47M people have dementia and global prevalence is rising, with recent estimates reaching 66M by 2030 and 131M by 2050. (Prince, et al., 2015) Dementia is a terminal syndrome characterized by severe cognitive deficits that interfere with activities of daily living. (Alzheimer's Association, 2017) Average survival time after diagnosis is 4.5 years and much of this time is spent in a state of disability requiring round-the-clock care. (Xie, Brayne, & Matthews, 2008) In 2017, $259B was spent on health and long-term care services associated with dementia and 18B hours of informal assistance worth $232B was provided by caregivers in the United States. (Alzheimer's Association, 2017).

Pervasive cognitive decline begins up to 30 years before clinical symptoms emerge in the nonnormative cognitive aging trajectory. (Singh-Manoux & Kivimaki, 2010) An intervention slowing cognitive decline could delay dementia onset and prevent up to 57% of the cases expected by 2050. (Alzheimer's Association, 2017) Risk modification early in the preclinical phase is our best hope for accomplishing this goal. However, preclinical dementia's asymptomatic nature makes it difficult to identify and it is unclear which risk factors (RFs) should be targeted in future interventions. (Fisher, Plassman, Heeringa, & Langa, 2008) Research focusing on modifiable RFs associated with early cognitive changes spanning a broad range of cognitive domains, especially those most affected by dementia, could inform early intervention efforts. These domains include Executive Function, Working Memory, Long-Term Memory, Reasoning and

Attention. To distinguish between normative and nonnormative cognitive aging processes within these and other domains, associations must be examined across adulthood.

1.2 Cardiovascular Health

The brain is a complex organ that accounts for only 2% of an adult's body weight but consumes 20-30% of total oxygen and nutrient supplies at rest. (Brown, 1999) The heart and arteries ensure adequate blood flow to the brain and cerebral blood vessels deliver blood and enable the trophic signaling that links cerebrovascular cells to the neurons and glia. (Iadecola, 2014) Cardiovascular disease (CVD) is a common age-related disease characterized by structural and functional disorder that interrupts these processes and is strongly implicated in the pathophysiology of the three most common dementia subtypes: AD, VaD and mixed AD/VaD. (Qui & Fratiglioni, 2015; Iadecola, 2014) Interventions targeting modifiable aspects of cardiovascular (CV) health could slow the early changes that characterize nonnormative cognitive aging and ultimately reduce the global dementia burden. However, additional research is needed to identify who and what to target before effective interventions can be developed and implemented successfully.

1.2.1 Aggregate Cardiovascular Risk

Up to 90% of CVD cases result from the aggregation of modifiable CV-RFs. (D'Agostino, et al., 2008) Multivariable screening tools have been developed based on this finding and are used to determine aggregate CV risk and guide treatment decisions in primary care settings. (Leening, Cook, & Ridker, 2017; O'Donnell, et al., 2010; Vasan, et al., 2005) These screening tools could also be used to identify adults early in the nonnormative cognitive aging trajectory when intervention would be most effective.

To determine which screening tool is best suited for this purpose, associations between multiple measures of aggregate CV risk and cognitive function must be examined across adulthood using a sample free from major cognitive impairment.

1.2.2 Modifiable Cardiovascular Risk Factors

Systolic blood pressure (BP), diastolic BP, fasting glucose and high density lipoprotein cholesterol (HDL-C) are promising intervention targets. Each major modifiable CV-RF has been previously associated with dementia, although their associations with early cognitive changes are unclear due to methodological differences between studies. (Kaffashian, et al., 2013; Qui & Fratiglioni, 2015) To determine whether systolic BP, diastolic BP, fasting glucose and HDL-C should be targeted in future interventions, each must be examined in association with cognitive function across adulthood using a sample free from major cognitive impairment.

1.2.3 Arterial Stiffness

Arterial stiffness is another promising intervention target. High modifiable CV risk stiffens the arteries and induces vascular alterations which damage the brain, especially in carriers of the apolipoprotein E (ApoE) ε4 allele. (Iulita, Noriega de la Colina, & Girouard, 2018; Mitchell, 2008) Arterial stiffness is relatively inexpensive to index using pulse wave velocity, the gold-standard indirect measure, and therapeutic strategies have been proposed to modulate stiffening processes. (Singer, Trollor, Baune, Sachdev, & Smith, 2014; Janić, Lunder, & Sabovič, 2014) However, it is important to treat the underlying cause of disease and the role of arterial stiffness in associations between modifiable CV risk and cognitive function is unclear. To remedy this, the mediating role of arterial stiffness in associations between modifiable CV risk and cognitive function

must be evaluated in adults with variable ApoE genotype using a sample free from major cognitive impairment.

1.3 Specific Aims

The objectives of this research are to determine whether: (i) Aggregate CV risk and major modifiable CV-RFs are associated with cognitive function across adulthood and; (ii) Arterial stiffness mediates these associations in adults with variable ApoE genotype. We propose three specific aims to accomplish these objectives. Each aim is addressed in a separate study.

Aim 1 (Chapter 2). Examine cross-sectional, prospective and longitudinal associations between aggregate CV risk and cognitive function across adulthood. The Framingham Risk Score (FRS) and the Maine Syracuse Longitudinal Study Cardiovascular Risk Factor Scale (MSLS-CVRFS) will be examined as measures of aggregate CV risk. Hypothesis 1. Higher FRS and MSLS-CVRFS will be associated with lower function across multiple cognitive domains and strength of each association will increase with advancing age.

Aim 2 (Chapter 3). Examine cross-sectional, prospective and longitudinal associations between major modifiable CV-RFs and cognitive function across adulthood. Systolic BP, diastolic BP, fasting glucose and HDL-C will be examined as modifiable CV-RFs. Hypothesis 2. Higher systolic BP, diastolic BP and fasting glucose and lower HDL-C will be associated with lower function across multiple cognitive domains and the strength of each association will increase with advancing age.

Aim 3 (Chapter 4). Examine arterial stiffness as a mediator of cross-sectional associations between modifiable CV risk and cognitive function in carriers and noncarriers of the ApoE ε4 allele. Systolic BP, diastolic BP, fasting glucose and HDL-C will

be examined as modifiable CV-RFs and the FRS and MSLS-CVRFS will be examined as measures of aggregate CV risk. Hypothesis 3. Higher arterial stiffness will mediate associations between higher modifiable CV risk and lower cognitive function and the mediating role of arterial stiffness will be strongest among carriers of the ApoE ε4 allele.

Chapter 2

ASSOCIATIONS BETWEEN AGGREGATE CARDIOVASCULAR RISK AND COGNITIVE FUNCTION: CROSS-SECTIONAL, PROSPECTIVE AND LONGITUINAL FINDINGS

2.1 Abstract

Background: Nonnormative cognitive aging is characterized by progressive cognitive decline and is a major contributor to global disability burden. Slowing cognitive decline early in the trajectory is vital to improving health and measures of aggregate CV risk could be used to screen for at risk adults. However, additional research is needed before such measures can be used as screening tools. This research examined associations between aggregate CV risk and cognitive function across adulthood.

Methods: Participants were community-dwelling adults (n=600) from Waves 6 and 7 of the Maine Syracuse Longitudinal Study (MSLS; M_{Age} 62.0±11.9 years; 61% female). FRS and MSLS-CVRFS were related to 9 cognitive domains in cross-sectional, prospective and longitudinal linear regression analyses. Age was examined as a moderator of each association.

Results: FRS and MSLS-CVRFS were negatively associated with cognitive function. Some associations were moderated by age, but most were observed for all participants. High FRS was associated with lower function in 5 domains in cross-sectional analyses and 3 domains in prospective analyses. High MSLS-CVRFS was associated with lower function in 8 domains in cross-sectional analyses and 7 domains in prospective analyses. High FRS and MSLS-CVRFS were associated with decline in 1 domain in longitudinal analyses. Cognitive domains most strongly associated with

aggregate CV risk were Global Cognition, Working Memory (WM) and Visual-Spatial Organization/Memory (VSOM).

Conclusion: High aggregate CV risk was associated with lower cognitive function. MSLS-CVRFS was a better predictor than the FRS. Further research is needed to confirm these findings and evaluate the MSLS-CVRFS as a screening tool for use in clinical settings.

2.2 Introduction

Complex cognitive changes accompany aging and it will become increasingly important to understand them as the number of adults over 65 years of age increases from 617M in 2015 to 1.6B in 2050. (He, Goodkind, & Kowal, 2016) Normative cognitive aging is characterized by subtle, but unavoidable cognitive decline that does not interfere with activities of daily living. (Harada, Love, & Triebel, 2013) Nonnormative cognitive aging is characterized by accelerated cognitive decline caused by disease that results in severe disability. The hallmark of nonnormative cognitive aging is dementia, a terminal syndrome that affects 47M people globally and costs >$1T per year. (Wimo, et al., 2017) Pervasive cognitive decline begins up to 30 years before the emergence of clinical symptoms in the trajectory (see Figure 1.1) and an intervention slowing decline could prevent up to 57% of the 131M dementia cases expected by 2050. (Alzheimer's Association, 2017; Singh-Manoux & Kivimaki, 2010) RF modification is our best hope for accomplishing this goal. However, adults at risk for dementia must be identified early in the nonnormative cognitive aging trajectory when intervention would be most effective and tools developed for this purpose have poor predictive accuracy. (Stephan, Kurth, Matthews, Brayne, & Dufouil, 2010)

CVD is the most common age-related disease (Roth, et al., 2017) and is strongly implicated in the pathophysiology of dementia (Qui & Fratiglioni, 2015; Kaffashian, et al., 2013). Exposure to modifiable CV-RFs accounts for up to 90% of cases and multivariable screening tools designed using routinely collected clinical data are often employed to determine aggregate CV risk and guide treatment decisions in primary care settings. (Leening, Cook, & Ridker, 2017; O'Donnell, et al., 2010; Vasan, et al., 2005) Several of these tools have also been used to predict cognitive outcomes with high accuracy (Kaffashian, et al., 2013; Harrison, et al., 2014) and could be used to identify adults early in the nonnormative cognitive aging trajectory when intervention would be most effective. Additional research is needed to confirm this hypothesis and to determine which screening tool is best suited for this purpose.

Each screening tool's ability to identify at risk adults could vary depending on individual characteristics, such as age, and the areas of cognitive function examined. Aging reflects greater intensity and duration of exposure to modifiable CV-RFs and could moderate associations between aggregate CV risk and cognitive function. (Kaffashian, et al., 2013; Vasan, et al., 2005) Participant age distributions are highly variable between previous studies and age is not typically accounted for as a moderation, making optimal screening timing unclear. Additional research is needed to determine where individuals are on the nonnormative cognitive aging trajectory and the rate at which decline occurs depending on aggregate CV risk.

State-of-the-art cognitive assessment includes examination of multiple cognitive abilities and arrangement of these abilities into different domains of cognitive function. (Elias, Torres, & Davey, 2018) Cognitive domains could be differentially affected by CV pathophysiology. However, literature linking CV and cognitive health is

characterized by over-reliance on imprecise neuropsychological tests that are insensitive to subtle cognitive change. (Elias, Torres, & Davey, 2018) Further, researchers often examine one or a few cognitive domains that are inconsistently selected between studies and examined using different research designs. To gain a better understanding of associations between aggregate CV risk and cognitive function, cross-sectional, prospective and longitudinal associations must be examined in a single study using a common set of cognitive outcomes.

The purpose of this research was to examine cross-sectional, prospective and longitudinal associations between aggregate CV risk and cognitive function across adulthood. The FRS and MSLS-CVRFS were examined. We hypothesized that higher FRS and MSLS-CVRFS would be associated with lower cognitive across multiple clinically important cognitive domains and that the strength of each association would increase with advancing age.

2.3 Methods

2.3.1 Study Design

Data for this research came from the MSLS, a 35-year study of CV and cognitive health in community-dwelling adults. Participants lived in Central New York at the time of recruitment. Initial exclusion criteria were alcoholism, diagnosis of a psychiatric illness and inability to comprehend English. Participants for this research had data on a broad array of CV-RFs obtained by objective measurement and completed a comprehensive neuropsychological test battery at Wave 6 (2001-2006) and Wave 7 (2006-2010).

The Wave 6 sample included 1084 participants. Due to changes in research funding, those who moved out of state (n=137) were not invited back at Wave 7 and an

additional 184 were lost to follow-up. Attrition was associated with higher aggregate CV risk, lower cognitive function and Black or other non-White race. Results of this research were not substantially influenced by attrition. Beginning with the 763 participants remaining after attrition, exclusions were made based on: (i) dementia diagnosis at Wave 6 (n=6); (ii) Parkinson's disease diagnosis at Wave 6 (n=1); (iii) stroke diagnosis at Wave 6 (n=15); (iv) active dialysis treatment at Wave 6 (n=2) and; (v) substantial missing data (n=139). The final sample included 600 participants.

Participants undergoing dialysis and those with history of dementia, Parkinson's disease or stroke were excluded based on our interested in examining associations between aggregate CV risk and longitudinal cognitive change in those without severe cognitive impairment. Dementia diagnosis was determined by a social psychologist, geriatric physician and two neuropsychologists using neuropsychological data, medical records and criteria from the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association. (McKhann, et al., 1984) Diagnostic decisions were recently confirmed using the International Classification of Diseases, 10th Edition, guidelines. (World Health Organization, 1992) Stroke was defined as an acute onset focal neurological deficit persisting for over 24 hours. Stroke and Parkinson's disease were self-reported and confirmed by medical history review.

The MSLS study protocol was developed in accordance with Declaration of Helsinki guidelines and approved by the Institutional Review Board at the University of Maine. Informed consent was obtained from all study participants prior to the collection of data.

2.3.2 Study Procedures

The Nutrition and Health Questionnaire (Riboli & Kaaks, 1997) was completed one week prior to laboratory testing. Demographic, socioeconomic and lifestyle characteristics were self-reported. Participants arrived for laboratory testing at 9:00 AM following a fast from midnight. Upon arrival, blood samples were collected. Automated BP assessment was performed following a 15-minute supine rest. A light breakfast was followed by a physical examination, medical history review and neuropsychological assessment. Participants were mailed a summary of their examination results one week after laboratory testing with a request that the contact their physician to review the report with them.

Smoking status (never, current or former) was self-reported via the Nutrition and Health Questionnaire. History of CVD (angina pectoris, coronary artery disease, myocardial infarction, heart failure or transient ischemic attack) was self-reported and confirmed by medical history review. Total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), HDL-C, triglyceride, glucose and creatinine (all mg/dL) as well as c-reactive protein (CRP, mg/L) and total homocysteine (tHcy, μmol/L) were obtained from a fasting blood sample using standard assay methods detailed by Elias et al. (2006). Diabetes mellitus was defined as self-reported treatment with antidiabetic medication or a fasting glucose level of ≥126 mg/dL. Estimated glomerular filtration rate (eGFR, mL/min/1.73m^2) was calculated using the four variable (creatinine, age, sex and ethnicity) Chronic Kidney Disease (CKD) Epidemiology Collaboration equation. (Levey, et al., 2009) Systolic and diastolic BP (both mmHg) assessment was automated (GE Critikon Dinamap Pro Care, oscillometric method) and consisted of 5 measurements each taken in the seated, recumbent and standing positions. Hypertension was defined as self-reported treatment with antihypertensive medication or averaged BP ≥140/90 mmHg.

Height (m) and weight (kg) were obtained by an examiner and used to calculate body mass index (BMI, kg/m^2).

2.3.3 Aggregate Cardiovascular Risk Scores

Aggregate CV risk was indexed using modified versions of the FRS and MSLS-CVRFS. Each measure of risk is point-based and calculated using major modifiable CV-RFs. Scoring schemes can be found in Table 2.1 and Table 2.2 and are described briefly below.

Recommended by the National Heart Lung and Blood Institute, the FRS is the most widely adopted screening tool for 10-year CVD risk around the world. (Dhingra & Vasan, 2012) Calculation of the FRS is sex-specific and based on: age (years), systolic BP (mmHg), TC (mg/dL), HDL-C (mg/dL), treatment with antihypertensive medication (yes vs no), smoking status (smoker vs nonsmoker) and diabetes mellitus (present vs absent). The inclusion of age in the FRS has been linked to inaccurate risk prediction and is thus controversial. Young adults with high modifiable risk tend to have low short-term but high lifetime risk estimates, which leads to undertreatment and missed opportunity for early intervention. (Leening, Cook, & Ridker, 2017) Further, short-term risk is overestimated in older adults due to completing causes of death, which leads to overtreatment, emotional stress and financial burden. (Dhingra & Vasan, 2012) With these considerations in mind, age was removed from FRS calculation in this research.

The MSLS-CVRFS is a screening tool that determines 5-year risk for mild cognitive impairment (MCI) based on an individual's current CV health. (Sullivan, 2017) Calculation of the MSLS-CVRFS is based on: hypertension (present vs absent), diabetes mellitus (present vs absent), history of CVD (yes vs no), obesity (BMI ≥ 30 vs <30),

ApoE genotype (1-2 vs 0 ε4 alleles), smoking status (smoker vs nonsmoker), low HDL-C (<40 vs ≥40 mg/dL), high LDL-C (>160 vs ≤160 mg/dL), high triglycerides (>200 vs ≤200 mg/dL), high tHcy (>13 vs ≤13 μmol/L), high CRP (>3 vs ≤3 mg/L) and low eGFR (<60 vs ≥60 mL/min/1.73m^2). ApoE genotype is not a modifiable CV-RF and was removed from MSLS-CVRFS calculation in this research.

Table 2.1. Modified Framingham Risk Score calculation.

Sex	**Points allotted**	**Systolic BP (mmHg) Untreated**	**Treated**	**TC (mg/dL)**	**HDL-C (mg/dL)**	**Smoker (yes vs no)**	**Diabetic (yes vs no)**
Female	-3	<120					
	-2				≥60		
	-1		<120		50-59		
	0	120-129		<160	45-49	No	No
	1	130-139		160-199	35-44		
	2	140-149	120-129		<35		
	3		130-139	200-239		Yes	
	4	150-159		240-279			Yes
	5	≥160	140-149	≥280			
	6		150-159				
	7		≥160				
Male	-2	<120			≥60		
	-1				50-59		
	0	120-129	<120	<160	45-49	No	No
	1	130-139		160-199	35-44		
	2	140-159	120-129	200-239	<35		
	3	≥160	130-139	240-279			Yes
	4		140-159	≥280		Yes	
	5		≥160				

Table 2.2. Modified Maine Syracuse Longitudinal Study Cardiovascular Risk Factor Scale calculation.

Variable	**Definition**	**Points allotted**
Hypertension	BP ≥140/90 or being treated with antihypertensive medication	1
Diabetes	Fasting glucose ≥126 mg/dL or being treated with antidiabetic medication	1
CVD	History of angina pectoris, coronary artery disease, myocardial infarction, heart failure and/or transient ischemic attack	1
Obesity	BMI ≥30	1
Smoker	Current cigarette smoker	1
Low HDL-C	HDL-C level <40 mg/dL	1
High LDL-C	LDL-C level >160 mg/dL	1
High triglycerides	Triglyceride level >200 mg/dL	1
High tHcy	tHcy level >13 µmol/L	1
High CRP	CRP level >3 mg/L	1
Low eGFR	eGFR level <60 mL/min	1

2.3.4 Cognitive Domain Scores

In contrast to most of the other data sources available, the MSLS included a comprehensive neuropsychological test battery containing 21 established tests and subscales indexing an array of cognitive abilities (Table 2.3). Several of these were combined in a previous study to produce four composite scores that each describe a domain of cognitive function: WM, Scanning and Tracking (ST), Verbal Episodic Memory (VEM) and VSOM. (Elias M. F., et al., 2009) The Similarities Test was also considered and was found to load on multiple factors. It is thus used as an individual test indexing Abstract Reasoning (AR). This research also includes other individual tests indexing General Mental State (GMS), Verbal Comprehension (VC) and Naming, as well as a Global Cognition domain created using all tests except for the Mini-Mental State Examination. Cognitive domain scores should be created using at least two cognitive tests in state-of-the-art assessment protocols. (Elias, Torres, & Davey, 2018) Several domains indexed by a single test were included in this research to make use of the full MSLS neuropsychological test battery.

To create cognitive domain scores: (i) raw test scores were standardized; (ii) the scores of tests used to define each domain were averaged, and; (iii) the averaged variables were re-standardized. A natural log transformation was applied to raw Trail Making Test scores prior to standardization. Transformed scores were also multiplied by -1 to reverse the scoring scheme. All domain scores have a mean of 0 and a standard deviation (SD) of 1. Higher domain scores indicate greater cognitive function.

Table 2.3. Maine-Syracuse Longitudinal Study neuropsychological test battery.

Cognitive test (by domain[a])	**Cognitive ability**
Abstract Reasoning	
Similarities[b]	Verbal intelligence and abstract reasoning
General Mental State	
Mini-Mental State Examination	Orientation, registration and attention
Naming	
Boston Naming Test	Ability to name common objects
Scanning and Tracking	
Trail Making A[c]	Visual scanning and tracking; concentration and attention
Trail Making B[c]	Trails A plus demands on executive functioning
Digit Symbol Substitution[b]	Psychomotor performance
Symbol Search[d]	Visual processing speed
Verbal Comprehension	
Information[b]	Knowledge of general information; demands on long-term memory
Verbal Episodic Memory	
Hopkins Verbal Learning Task	Verbal learning and memory
Logical Memory: Immediate Recall[e]	Immediate verbal memory
Logical Memory: Delayed Recall[e]	Delayed verbal memory
Visual-Spatial Organization/Memory	
Block Design[b]	Visual-spatial perception, organization and construction
Hoper Visual Organization Test	Visual-spatial organization plus demands on executive functioning
Matrix Reasoning[d]	Abstract reasoning and pattern recognition
Object Assembly[b]	Speed of visual-spatial organization
Visual Reproduction: Immediate Recall[e]	Visual-spatial problem solving, immediate recall and visual memory
Visual Reproduction: Delayed Recall[e]	Visual-spatial problem solving, delayed recall and visual memory
Working Memory	
Controlled Oral Word Association Test	Verbal fluency and executive functioning
Digit Span: Forward[b]	Attention and concentration
Digit Span: Backward[b]	Attention, concentration and working memory
Letter-Number Sequence[d]	Information processing while holding information in memory

[a]Global Cognition (not listed) includes all tests except for the Mini-Mental State Examination.
[b]Origin: Wechsler Adult Intelligence Scale. (Wechsler, 1955)
[c]Origin: Halstead-Reitan Neuropsychological Test Battery. (Reitan & Wolfson, 1993)
[d]Origin: Wechsler Adult Intelligence Scale III. (Wechsler, 1997)
[e]Origin: Wechsler Memory Scale-Revised. (Wechsler, 1987)

2.3.5 Statistical Analyses

Stata/MP 15.1 (College Station, TX: StataCorp LLC) was used to perform all statistical analyses. Descriptive statistics are presented as percentages for categorical variables and means ± SDs for continuous variables. Multiple linear regression models with bootstrapped confidence intervals (1000 replicate samples) were employed to account for potential non-normal distributions. FRS and MSLS-CVRFS were examined as predictors of each cognitive domain score in three sets of analyses:

(i) Cross-sectional: W6 Cognition = W6 CV risk + W6 covariates

(ii) Prospective: W7 Cognition = W6 CV risk + W6 covariates

(iii) Longitudinal: W7 Cognition = W6 CV risk + W6 covariates + W6 Cognition

Covariates were age, sex, education and ethnicity. Age was also examined as a moderator of associations between each measure of aggregate CV risk and cognitive domain score. Longitudinal change in cognitive function was assessed using the residualized change approach, in which an outcome (e.g., Wave 7 VC) is regressed upon itself at a previous occasion (e.g., Wave 6 VC). For further detail on the residualized change approach, see work by Castro-Schilo and Grimm (2018).

2.4 Results

2.4.1 Participant Characteristics

Demographic and health characteristics of study participants (n=600) at Wave 6 and Wave 7 are displayed in Table 2.4. Participants were predominantly White females. Participants were predominantly middle-aged and well educated at Wave 6. Mean systolic BP was high and TC was borderline high. Mean CRP was indicative of high CV

risk, eGFR of Stage 2 CKD and BMI of overweight status. Mean diastolic BP, fasting glucose, LDL-C, HDL-C, triglyceride and tHcy levels were normal. Mean FRS (range: -5 to 15) and MSLS-CVRFS (range: 0 to 9) were indicative of low to moderate aggregate CV risk. The majority of participants did not have CVD or diabetes, had hypertension, were not receiving antihypertensive treatment and were not smokers.

Age and diastolic BP increased significantly between Wave 6 and Wave 7. A significant increase in the prevalence of CVD, diabetes, hypertension and antihypertensive treatment was also observed. TC, LDL-C, HDL-C, triglyceride and eGFR levels, as well as the prevalence of cigarette smoking decreased significantly between waves. No other significant differences in participant characteristics were observed.

Table 2.4. Participant characteristics at Wave 6 and Wave 7 (n=600).

Variable	Wave of the MSLS		P-value
	6	7	
Age (years)	62.0 (11.9)	66.7 (11.8)	<0.001
Education (years)	14.7 (2.7)	14.7 (2.8)	0.342
Systolic BP (mmHg)	130.3 (21.5)	130.8 (20.4)	0.550
Diastolic BP (mmHg)	70.1 (9.8)	76.8 (9.7)	<0.001
Fasting glucose (mg/dL)	98.9 (29.0)	98.9 (26.1)	0.978
TC (mg/dL)	202.9 (39.6)	186.9 (39.8)	<0.001
LDL-C (mg/dL)	121.4 (33.4)	111.3 (33.1)	<0.001
HDL-C (mg/dL)	54.3 (15.6)	52.6 (15.3)	<0.001
Triglycerides (mg/dL)	134.9 (83.0)	116.9 (76.0)	<0.001
CRP (mg/L)[a]	4.0 (4.6)	-	-
eGFR (mL/min/1.73m^2)	78.0 (16.2)	65.5 (15.5)	<0.001
tHcy (μmol/L)	9.6 (3.2)	10.5 (3.6)	0.170
BMI (kg/m^2)	29.5 (6.0)	29.7 (6.6)	<0.001
FRS (points)	3.4 (3.9)	3.4 (3.9)	0.835
MSLS-CVRFS (points)[b]	2.4 (1.7)	2.3 (1.7)	0.202
	Percent		
Sex (female)[c]	61.0	-	-
Race (White)[c]	93.0	-	-
CVD (yes)	13.0	18.0	<0.001
Diabetic (yes)	11.0	16.0	<0.001
Hypertensive (yes)	59.0	66.0	<0.001
Treated for high BP (yes)	48.0	59.0	<0.001
Smoker (yes)	40.0	39.0	<0.001

[a]CRP was not assessed at Wave 7.
bCRP was not included in MSLS-CVRFS calculation at Wave 7.
cDid not change between Wave 6 and 7.

2.4.2 Primary Analyses

Findings of statistical analyses are reported in Tables 2.5 through 2.7. Standardized (β) and unstandardized (b) regression coefficients reflect the adjusted change in each cognitive domain score per 1 SD and 1 point increase in each measure of aggregate CV risk, respectively. As domain scores are standardized, coefficients are reported in the z-score metric.

Table 2.5 displays the results of cross-sectional analyses examining associations between Wave 6 aggregate CV risk and Wave 6 cognitive function. FRS was negatively associated with Global Cognition (P=0.014), GMS (P=0.037), AR (P=0.008), VSOM (P=0.022) and WM (P=0.046) in main effects models. In interaction models, FRS × age was negatively associated with VSOM (P=0.010). MSLS-CVRFS was negatively associated with Global Cognition (P<0.001), GMS (P=0.002), AR (P<0.001), VSOM (P=0.001), Naming (P=0.015), ST (P=0.007), VC (P=0.007) and WM (P=0.014) in main effects models. In interaction models, MSLS-CVRFS × age was negatively associated with AR (P=0.027) and positively associated with WM (P=0.018).

Table 2.6 displays the results of prospective analyses examining associations between Wave 6 aggregate CV risk and Wave 7 cognitive function. FRS was negatively associated with Global Cognition (P=0.046), VSOM (P=0.033) and WM (P=0.010) in main effects models. Figure 2.1 illustrates the prospective association between FRS and WM. In interaction models, FRS × age was not associated with any cognitive domain. MSLS-CVRFS was negatively associated with Global Cognition (P<0.001), AR (P=0.001), VSOM (P=0.003), Naming (P=0.031), ST (P=0.003), VC (P=0.012) and WM (P<0.001) in main effects models. Figure 2.2 illustrates the prospective association

between MSLS-CVRFS and WM. In interaction models, MSLS-CVRFS × age was not associated with any cognitive domain.

Table 5 displays the results of longitudinal analyses examining associations between Wave 6 aggregate CV risk and residualized cognitive change between Wave 6 and Wave 7. FRS was not associated with residualized change in any cognitive domain in main effects models. In interaction models, FRS × age was associated with decline in Naming (P=0.008). MSLS-CVRFS was associated with decline in WM (P=0.001) in main effects models. In interaction models, MSLS-CVRFS × age was not associated with residualized change in any cognitive domain

Table 2.5. Results of cross-sectional analyses examining associations between Wave 6 aggregate cardiovascular risk and Wave 6 cognitive function.

Measure of risk	Measure	Cognitive domain								
		Global	**GMS**	**AR**	**VSOM**	**Naming**	**ST**	**VC**	**VEM**	**WM**
FRS	β	-0.0717*	-0.0855*	-0.0928**	-0.0779*	-0.0377	-0.0291	-0.0547	-0.0161	-0.0750*
	b	-0.0184	-0.0219	-0.0237	-0.0199	-0.0096	-0.0075	-0.0140	-0.0041	-0.0192
	95% LCL	-0.0329,	-0.0425,	-0.0413,	-0.0370,	-0.0258,	-0.0246,	-0.0319,	-0.0226,	-0.0381,
	95% UCL	-0.0038	-0.0013	-0.0062	-0.0029	0.0065	0.0097	0.0039	0.0143	-0.0003
	P-value	0.014	0.037	0.008	0.022	0.243	0.393	0.125	0.661	0.046
FRS × age	β	-0.1688	-0.2420	-0.3006	-0.4843*	-0.0036	-0.1478	-0.0255	0.1098	0.2342
	b	-0.0007	-0.0010	-0.0012	-0.0019	0.0000	-0.0006	-0.0001	0.0004	0.0009
	95% LCL	-0.0021,	-0.0027,	-0.0026,	-0.0034,	-0.0017,	-0.0021,	-0.0018,	-0.0011,	-0.0008,
	95% UCL	0.0007	0.0007	0.0002	-0.0005	0.0016	0.0009	0.0016	0.0019	0.0026
	P-value	0.343	0.266	0.101	0.010	0.986	0.435	0.905	0.570	0.285
MSLS-CVRFS	β	-0.1244***	-0.1197**	-0.1609***	-0.1098**	-0.0879*	-0.0886**	-0.0940**	-0.0503	-0.1000*
	b	-0.0749	-0.0720	-0.0969	-0.0661	-0.0531	-0.0533	-0.0566	-0.0303	-0.0602
	95% LCL	-0.1101,	-0.1181,	-0.1368,	-0.1055,	-0.0959,	-0.0921,	-0.0975,	-0.0750,	-0.1081,
	95% UCL	-0.0397	-0.0260	-0.0570	-0.0268	-0.0102	-0.0146	-0.0158	0.0144	-0.0123
	P-value	<0.001	0.002	<0.001	0.001	0.015	0.007	0.007	0.184	0.014
MSLS-CVRFS × age	β	0.1207	-0.3007	-0.4034*	-0.0190	0.0415	0.0623	0.1123	0.0580	0.5257*
	b	0.0011	-0.0028	-0.0037	-0.0002	0.0004	0.0006	0.0010	0.0005	0.0048
	95% LCL	-0.0021,	-0.0065,	-0.0070,	-0.0036,	-0.0040,	-0.0028,	-0.0026,	-0.0033,	0.0008,
	95% UCL	0.0044	0.0010	-0.0004	0.0032	0.0048	0.0039	0.0046	0.0044	0.0088
	P-value	0.505	0.151	0.027	0.920	0.865	0.737	0.576	0.787	0.018

*P<0.050; **P<0.010; ***P<0.001.

Table 2.6. Results of prospective analyses examining associations between Wave 6 aggregate cardiovascular risk and Wave 7 cognitive function.

Measure of risk	Measure	Cognitive domain								
		Global	**GMS**	**AR**	**VSOM**	**Naming**	**ST**	**VC**	**VEM**	**WM**
FRS	β	-0.0717*	-0.0304	-0.0563	-0.0667*	-0.0379	-0.0300	-0.0393	-0.0056	-0.0956*
	b	-0.0159	-0.0078	-0.0144	-0.0170	-0.0097	-0.0077	-0.0101	-0.0014	-0.0244
	95% LCL	-0.0316,	-0.0277,	-0.0322,	-0.0327,	-0.0245,	-0.0231,	-0.0276,	-0.0194,	-0.0430,
	95% UCL	-0.0003	0.0121	0.0034	-0.0014	0.0052	0.0078	0.0075	0.0165	-0.0059
	P-value	0.046	0.444	0.114	0.033	0.201	0.329	0.261	0.875	0.010
FRS × age	β	-0.2002	-0.2020	-0.1901	-0.2861	-0.3294	-0.1056	-0.0750	-0.1041	-0.0680
	b	-0.0008	-0.0008	-0.0008	-0.0011	-0.0013	-0.0004	-0.0003	-0.0004	-0.0003
	95% LCL	-0.0022,	-0.0026,	-0.0023,	-0.0026,	-0.0027,	-0.0018,	-0.0020,	-0.0020,	-0.0019,
	95% UCL	0.0006	0.0010	0.0008	0.0003	0.0001	0.0009	0.0014	0.0012	0.0014
	P-value	0.255	0.369	0.336	0.123	0.072	0.541	0.726	0.606	0.745
MSLS-CVRFS	β	-0.1244***	-0.0679	-0.1249**	-0.0977**	-0.0908*	-0.0990**	-0.0960*	-0.0492	-0.1613***
	b	-0.0761	-0.0409	-0.0752	-0.0588	-0.0547	-0.0596	-0.0578	-0.0296	-0.0971
	95% LCL	-0.1137,	-0.0875,	-0.1203,	-0.0980,	-0.1043,	-0.0985,	-0.1029,	-0.0743,	-0.1449,
	95% UCL	-0.0384	0.0057	-0.0300	-0.0196	-0.0050	-0.0207	-0.0127	0.0150	-0.0493
	P-value	<0.001	0.086	0.001	0.003	0.031	0.003	0.012	0.194	<0.001
MSLS-CVRFS × age	β	0.0372	0.0882	-0.2356	0.0436	-0.1677	0.0379	0.0077	-0.1665	0.2884
	b	0.0003	0.0008	-0.0022	0.0004	-0.0015	0.0003	0.0001	-0.0015	0.0026
	95% LCL	-0.0030,	-0.0032,	-0.0056,	-0.0033,	-0.0057,	-0.0030,	-0.0037,	-0.0056,	-0.0010,
	95% UCL	0.0037	0.0048	0.0013	0.0041	0.0026	0.0037	0.0038	0.0025	0.0063
	P-value	0.841	0.689	0.222	0.833	0.470	0.839	0.971	0.458	0.156

*P<0.050; **P<0.010; ***P<0.001.

Table 2.7. Results of longitudinal analyses examining associations between Wave 6 aggregate cardiovascular risk and residualized cognitive change between Waves 6 and 7.

Measure of risk	Measure	Cognitive domain								
		Global	**GMS**	**AR**	**VSOM**	**Naming**	**ST**	**VC**	**VEM**	**WM**
FRS	β	-0.0014	0.0096	-0.0002	-0.0067	0.0187	-0.0079	0.0060	0.0049	-0.0385
	b	-0.0004	0.0025	0.0000	-0.0017	0.0039	-0.0020	0.0015	0.0013	-0.0098
	95% LCL	-0.0076,	-0.0140,	-0.0146,	-0.0112,	-0.0050,	-0.0107,	-0.0092,	-0.0111,	-0.0215,
	95% UCL	0.0069	0.0189	0.0145	0.0078	0.0128	0.0066	0.0123	0.0137	0.0019
	P-value	0.921	0.770	0.996	0.725	0.390	0.645	0.779	0.841	0.099
FRS × age	β	-0.0570	-0.0888	-0.0088	0.0874	-0.4011**	0.0065	-0.0539	-0.1762	-0.2469
	b	-0.0002	-0.0004	0.0000	0.0003	-0.0013	0.0000	-0.0002	-0.0007	-0.0010
	95% LCL	-0.0009,	-0.0018,	-0.0013,	-0.0005,	-0.0023,	-0.0008,	-0.0012,	-0.0017,	-0.0021,
	95% UCL	0.0005	0.0011	0.0012	0.0012	-0.0003	0.0008	0.0007	0.0003	0.0002
	P-value	0.520	0.641	0.956	0.418	0.008	0.948	0.658	0.188	0.094
MSLS-CVRFS	β	-0.0213	-0.0123	-0.0280	-0.0133	0.0313	-0.0322	-0.0183	-0.0162	-0.0857**
	b	-0.0128	-0.0074	-0.0169	-0.0080	0.0155	-0.0194	-0.0110	-0.0098	-0.0516
	95% LCL	-0.0319,	-0.0470,	-0.0548,	-0.0316,	-0.0062,	-0.0411,	-0.0376,	-0.0398,	-0.0824,
	95% UCL	0.0063	0.0322	0.0211	0.0156	0.0372	0.0024	0.0156	0.0202	-0.0208
	P-value	0.189	0.714	0.385	0.506	0.162	0.081	0.418	0.523	0.001
MSLS-CVRFS × age	β	-0.0648	0.2284	0.0070	0.0582	-0.1180	-0.0091	-0.0852	-0.2045	-0.1098
	b	-0.0006	0.0021	0.0001	0.0005	-0.0009	-0.0001	-0.0008	-0.0019	-0.0010
	95% LCL	-0.0023,	-0.0014,	-0.0026,	-0.0015,	-0.0032,	-0.0020,	-0.0027,	-0.0045,	-0.0037,
	95% UCL	0.0011	0.0056	0.0027	0.0026	0.0014	0.0018	0.0011	0.0007	0.0017
	P-value	0.490	0.240	0.962	0.608	0.450	0.931	0.428	0.158	0.465

*P<0.050; **P<0.010; ***P<0.001.

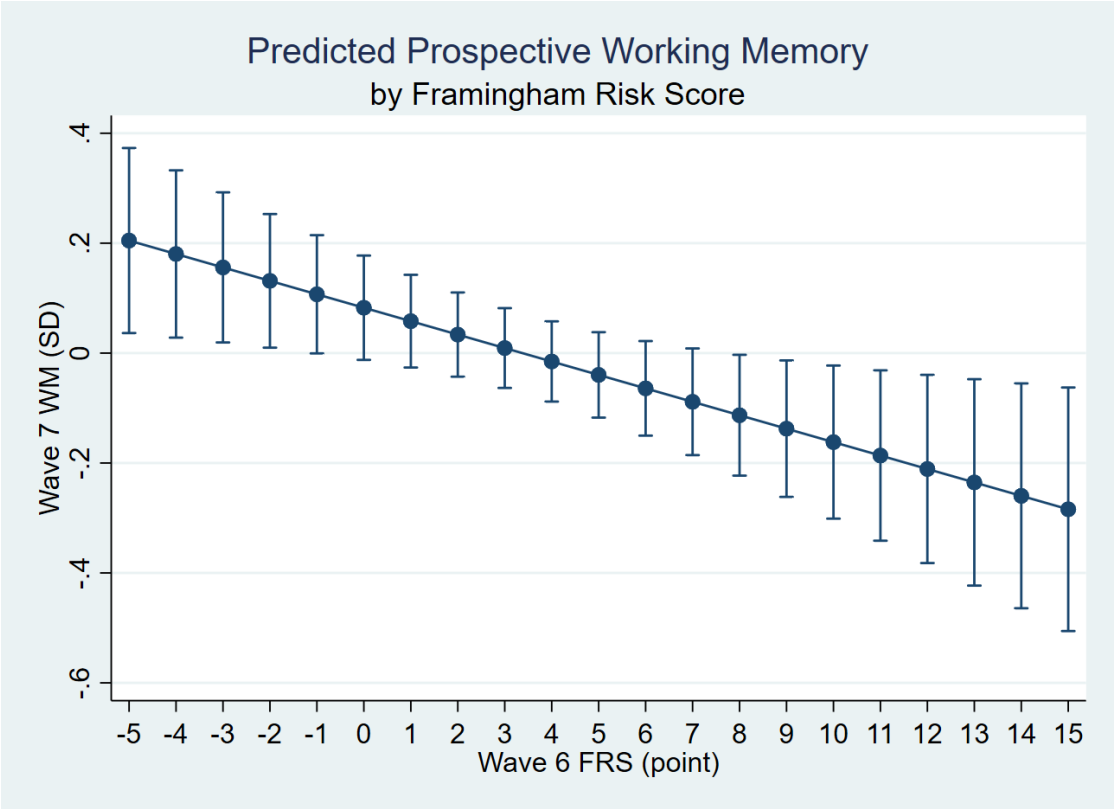

Figure 2.1. Framingham Risk Score as a predictor of Working Memory in prospective analyses.

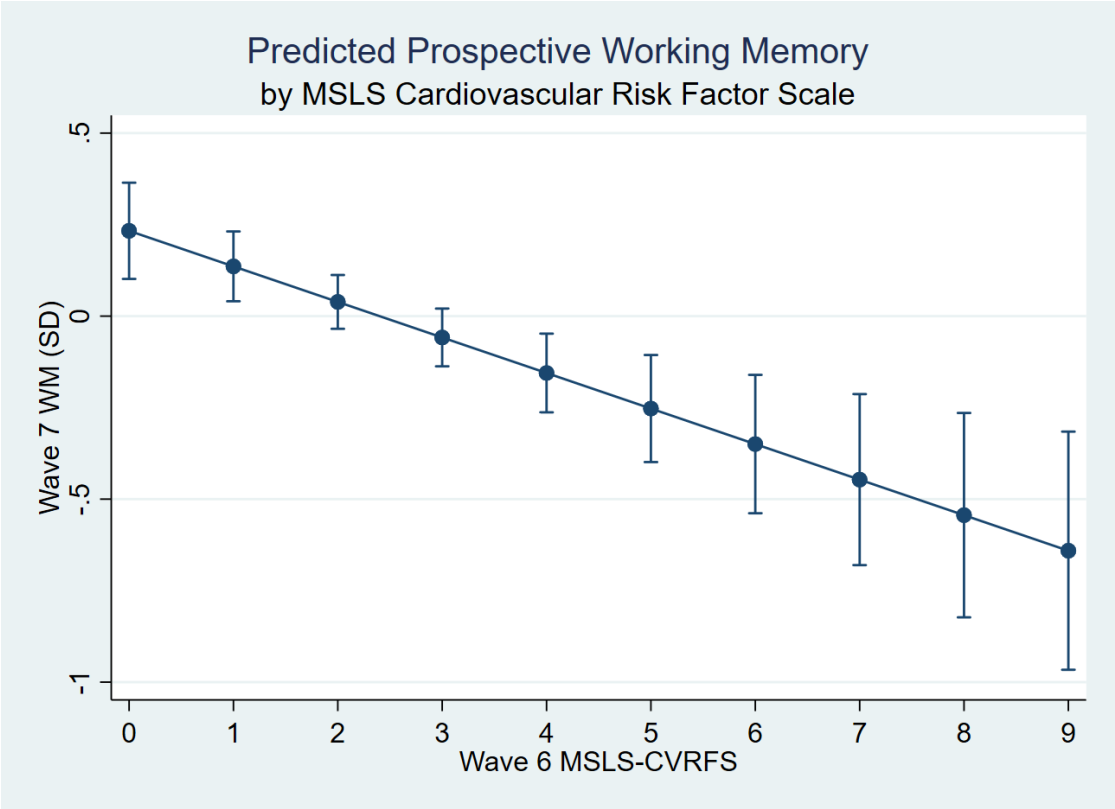

Figure 2.2. Maine Syracuse Longitudinal Study Cardiovascular Risk Factor Scale as a predictor of Working Memory in prospective analyses.

2.5 Discussion

Few research studies examining the role of aggregate CV risk in the nonnormative cognitive aging trajectory have been conducted to date. We have attempted to expand the literature by providing a comprehensive examination of cross-sectional, prospective and longitudinal associations between aggregate CV risk and cognitive function in this research. Measures of aggregate CV risk examined where FRS and MSLS-CVRFS, each of which was negatively associated with several cognitive domains. Some associations were observed using the entire sample of MSLS participants, while others were significant only in the context of advancing age.

High FRS has been associated with grey matter atrophy, frontotemporal cortex thinning and high burden of cerebral amyloid-β in previous research, each of which is a pathophysiological mechanism underlying the nonnormative cognitive aging trajectory. (Cardenas, et al., 2012; Reed, et al., 2012; Villeneuve, et al., 2014) In accordance with these findings, cross-sectional research by Joosten et al. (2013) found that higher FRS was associated with lower Executive Function and Memory in midlife and late life. Higher FRS in midlife was also associated with longitudinal decline in Global Cognition, Reasoning and Vocabulary in the Whitehall II Study (Kaffashian, et al., 2013) and higher FRS in late life was associated with longitudinal decline in Global Cognition and Memory in the English Longitudinal Study of Ageing. (Dregan, Stewart, & Gulliford, 2013) In cross-sectional analyses we found that each 1 SD of higher FRS (4 points) was associated with 0.07-0.9 SD lower Global Cognition, GMS, AR, VSOM and WM and each 1 SD of higher FRS × age (12 years) was associated with 0.48 SD lower VSOM. In prospective analyses we found that each 1 SD of higher FRS was associated with 0.07-0.10 SD lower Global Cognition, VSOM and WM. Lastly, in longitudinal analyses

we found that each 1 SD of higher FRS × age was associated with 0.40 SD decline in Naming.

The relationship between MSLS-CVRFS and brain structure has not yet been examined and only one study to date has examined the MSLS-CVRFS as a predictor of cognitive function. Sullivan (Sullivan, 2017) found that higher MSLS-CVRFS was prospectively associated with lower Global Cognition, ST, VSOM and WM in the MSLS. However, Sullivan (Sullivan, 2017) did not examine all of the cognitive domains indexed by the MSLS neuropsychological test battery, age was not examined as a moderator and cross-sectional and longitudinal analyses were not performed. In cross-sectional analyses we found that each 1 SD of higher MSLS-CVRFS (2 points) was associated with 0.09-0.20 SD lower Global Cognition, GMS, AR, VSOM, Naming, ST, VC and WM and each 1 SD of higher MSLS-CVRFS × age was associated with 0.40 SD lower AR and 0.53 SD higher WM. In prospective analyses we found that each 1 SD of higher MSLS-CVRFS was associated with 0.09-0.20 SD lower Global Cognition, AR, VSOM, Naming, ST, VC and WM. Lastly, in longitudinal analyses we found that each 1 SD of higher MSLS-CVRFS was associated with 0.90 SD lower WM.

The FRS and MSLS-CVRFS utilize data on similar modifiable CV-RFs obtained from medical history review, BP assessment and blood assays. Both measures of aggregate CV risk predicted lower function across multiple cognitive domains in our study. The MSLS-CVRFS is newer and has been examined in few studies compared with the FRS but was found to be the superior predictor. Additional research is needed to replicate and extend these findings before the MSLS-CVRFS can be used to identify adults at risk for cognitive decline early in the nonnormative cognitive aging trajectory and guide treatment decisions in primary care settings.

2.5.1 Study Limitations

The pathophysiological mechanisms linking aggregate CV risk and cognitive function are not fully understood in the literature. The MSLS did not include brain imaging, which would have provided us with the data necessary to conduct an in-depth examination of these mechanisms. Attrition between Wave 6 and Wave 7 was high and the use of longitudinal data resulted in the loss of a substantial number of participants. However, attrition patterns were evaluated and were not found to substantially alter the results of this research. Longitudinal findings observed in this research were limited, which could be the result of the short follow-up period between Wave 6 and Wave 7. Results presented in this research are likely conservative, as participants of the MSLS were well educated and education protects against cognitive decline through increased cognitive reserve. (Meng & D'Arcy, 2012)

2.5.2 Study Strengths

The design of the MSLS permitted us to examine cross-sectional, prospective and longitudinal associations between aggregate CV risk and cognitive function in a community-dwelling sample of adults who were not selected for CVD or cognitive impairment. Two measures of aggregate CV risk and an extensive neuropsychological test battery indexing multiple cognitive domains were included. Associations were examined across adulthood using three commonly employed study designs. To our knowledge, this is one of the most comprehensive examinations of aggregate CV risk and cognitive function in the literature to date.

2.6 Conclusion

Significant cross-sectional, prospective and longitudinal associations were observed between aggregate CV risk and cognitive function. FRS and MSLS-CVRFS were negatively associated with cognitive function. While some associations were observed for all study participants, others were observed only in the context of advancing age. Additional research is needed to confirm and extend these findings before the FRS and MSLS-CVRFS can be used to identify at risk adults in primary care settings. Additional research is also needed to determine which modifiable CV-RFs should be treated in order to slow nonnormative cognitive aging in future interventions.

Chapter 3

ASSOCIATIONS BETWEEN MODIFIABLE CARDIOVASCULAR RISK FACTORS AND COGNITIVE FUNCTION: CROSS-SECTIONAL, PROSPECTIVE AND LONGITUDINAL FINDINGS

3.1 Abstract

Background: Nonnormative cognitive aging is characterized by progressive cognitive decline and is a major contributor to global disability burden. Slowing cognitive decline early in the trajectory is vital to improving health and modifiable CV-RFs are promising intervention targets. However, additional research is needed before effective interventions can be developed. This research examined associations between major modifiable CV-RFs and cognitive function across adulthood.

Methods: Participants were community-dwelling adults (n=600) from Waves 6 and 7 of the MSLS (M_{Age} 62.0±11.9 years; 61% female). Using linear regression, systolic BP, diastolic BP, fasting glucose and HDL-C were related to 9 cognitive domains in cross-sectional, prospective and longitudinal linear regression analyses. Age was examined as a moderator of each association.

Results: Systolic BP, diastolic BP and fasting glucose were negatively associated with cognitive function and HDL-C was positively associated with cognitive function. Some associations were observed for all participants, while others were moderated by age. HDL-C was the best predictor of cross-sectional and prospective cognitive function, while systolic BP × age and diastolic BP × age were the best predictors of longitudinal decline. Cognitive domains most strongly associated with modifiable CV-RFs were Global Cognition, WM and VSOM.

Conclusion: Modifiable CV-RFs were associated with lower cognitive function. High systolic and diastolic BP, in the context of advancing age, and low HDL-C were especially important in this context. Further research is needed to confirm these findings, explore the pathophysiological mechanisms underlying each association and determine how best to intervene in order to slow nonnormative cognitive aging.

3.2 Introduction

Complex cognitive changes accompany aging and it will become increasingly important to understand them as the number of adults over 65 years of age increases from 617M in 2015 to 1.6B in 2050. (He, Goodkind, & Kowal, 2016) Normative cognitive aging is characterized by subtle, but unavoidable cognitive decline that does not interfere with activities of daily living. (Harada, Love, & Triebel, 2013) Nonnormative cognitive aging is characterized by accelerated cognitive decline caused by disease that results in severe disability. The hallmark of nonnormative cognitive aging is dementia, a terminal syndrome that affects 47M people globally and costs >$1T per year. (Wimo, et al., 2017) Pervasive cognitive decline begins up to 30 years before the emergence of clinical symptoms in the trajectory (see Figure 1.1) and an intervention slowing decline could prevent up to 57% of the 131M dementia cases expected by 2050. (Alzheimer's Association, 2017; Singh-Manoux & Kivimaki, 2010) RF modification early in the nonnormative cognitive aging trajectory is our best hope for accomplishing this goal. However, no standard, evidence-based interventions currently exist.

CVD is the most common age-related disease, affecting >423M people and accounting for one-third of all global deaths. (Roth, et al., 2017) Up to 90% of cases are caused by exposure to modifiable CV-RFs, which are strictly monitored and treated in primary care settings as a result. (O'Donnell, et al., 2010) CVD is strongly implicated

in the pathophysiology dementia (Qui & Fratiglioni, 2015; Kaffashian, et al., 2013) and interventions targeting modifiable CV-RFs could slow nonnormative cognitive aging and ultimately reduce dementia burden. High systolic BP, diastolic BP and fasting glucose and low HDL-C are promising intervention targets. However, their precise roles and the importance of their timing in the nonnormative cognitive aging trajectory differ between studies.

Disparate research findings could be explained by key differences in participant characteristics and study design. Advancing age reflects higher aggregation, intensity and duration of exposure to modifiable CV-RFs and could moderate associations between modifiable CV-RFs and cognitive function. (Kaffashian, et al., 2013; Vasan, et al., 2005) Participant age distributions are highly variable between previous studies and age is not typically accounted for as a moderator, making optimal intervention timing unclear. Additional research is needed to determine where individuals are on the nonnormative cognitive aging trajectory and the rate at which decline occurs depending on exposure to modifiable CV-RFs.

State-of-the-art cognitive assessment includes examination of multiple cognitive abilities through neuropsychological assessment and arrangement of these abilities into cognitive domains. (Elias, Torres, & Davey, 2018) Literature linking CV and cognitive health is characterized by over-reliance on imprecise neuropsychological tests that are insensitive to subtle cognitive change. (Elias, Torres, & Davey, 2018; Singer, Trollor, Baune, Sachdev, & Smith, 2014) Furthermore, researchers often examine one or a few cognitive domains that are inconsistently selected between studies and examined using different research designs. To gain a better understanding of associations between modifiable CV-RFs and cognitive function, cross-sectional, prospective and longitudinal

associations must be examined in a single study using a common set of cognitive outcomes.

The purpose of this research was to examine cross-sectional, prospective and longitudinal associations between major modifiable CV-RFs and cognitive function across adulthood. Systolic BP, diastolic BP, fasting glucose and HDL-C were examined. We hypothesized that higher systolic BP, diastolic BP and fasting glucose and lower HDL-C would be associated with lower function across multiple clinically important cognitive domains and that the strength of each association would increase with advancing age.

3.3 Methods

3.3.1 Study Design

Data for this research came from the MSLS. The MSLS was a 35-year study of aging, CV risk and cognitive function. Participants were community-dwelling adults living in Central New York at the time of recruitment. Initial exclusion criteria were diagnosis of psychiatric illness, alcoholism and inability to comprehend English. Participants for this research completed comprehensive neuropsychological assessment and had data on major CV-RFs obtained by objective measurement at Wave 6 (2001-2006) and Wave 7 (2006-2010).

The sample at Wave 6 included 1084 participants. Individuals who moved out of state (n=137) were not invited back at Wave 7 due to changes in research funding and an additional 184 were lost to follow-up. Attrition was associated with lower cognitive function, higher aggregate CV risk and Black or other non-White race. Results of this research were not substantially influenced by attrition. Beginning with the 763 participants who remained after attrition, individuals were excluded based on: (i) active

dialysis treatment at Wave 6 (n=2); (ii) dementia diagnosis at Wave 6 (n=6); (iii) stroke diagnosis at Wave 6 (n=15); (iv) Parkinson's disease diagnosis at Wave 6 (n=1) and; (v) substantial missing data (n=139). The final sample consisted of 600 participants.

Participants undergoing dialysis and those with history of dementia, stroke or Parkinson's disease at Wave 6 were excluded based on our interest in examining associations between modifiable CV-RFs and longitudinal cognitive change in those without severe cognitive impairment. Clinical diagnoses of dementia were determined by two neuropsychologists, a geriatric physician and a social psychologist using neuropsychological data, medical records and criteria from the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association. (McKhann, et al., 1984) Diagnostic decisions were recently confirmed using the International Classification of Diseases, 10th Edition, guidelines. (World Health Organization, 1992) Stroke was defined as a focal neurological deficit of acute onset persisting for over 24 hours. History of stroke and Parkinson's disease were self-reported and confirmed by medical history review.

The protocol for this study was developed in accordance with the guidelines established by the Declaration of Helsinki and was approved by the University of Maine Institutional Review Board. Informed consent was obtained from all study participants prior to data collection.

3.3.2 Study Procedures

Demographic, socioeconomic and lifestyle characteristics were self-reported using the Nutrition and Health Questionnaire (Riboli & Kaaks, 1997) one week prior to laboratory testing. Laboratory testing began at 9:00 AM following a fast from midnight. Blood samples were collected upon arrival followed by a 15-minute supine rest and

automated BP assessment. Physical examinations with medical history review were conducted following a light breakfast. Laboratory testing concluded with the administration of a neuropsychological test battery. One week after laboratory testing, participants were mailed a summary of their medical and neuropsychological examinations with the request that they contact a physician to review the report with them.

Glucose and HDL-C (both mg/dL) were obtained from a fasting blood sample using standard assay methods detailed by Elias et al. (2006). Systolic and diastolic BP (both mmHg) assessment was automated (GE Critikon Dinamap Pro Care, oscillometric method) and consisted of 5 measurements each taken in the seated, recumbent and standing positions. In this research, BP variables used in primary statistical analyses were the average of all 15 measurements. Sensitivity analyses were also performed in which these BP variables were replaced with ones based on the 5 seated measurements alone, as BP is typically assessed with individuals in the seated position.

3.3.3 Cognitive Domain Scores

The MSLS neuropsychological test battery is one of the largest used in the literature to date. It contains 21 established tests and subscales used to index a wide range of cognitive abilities (Table 2.3). Several of these have been combined by Elias et al. (2009) via factor analysis to produce four cognitive domains: VEM, WM, ST and VSOM. Elias et al. (2009) also considered the Similarities Test, which was found to load on multiple factors and is used as an individual test indexing AR. This research also includes other individual tests indexing VC, Naming and GMS, as well as a domain of Global Cognition created using all tests except for the Mini-Mental State Examination. Ideally, cognitive domain scores should be created using at least two cognitive

tests. (Elias, Torres, & Davey, 2018) This research included several domains indexed by a single test to make use of the full MSLS neuropsychological test battery.

Cognitive domain scores were created by standardizing raw test scores, averaging the scores of tests used to define each domain and re-standardizing the averaged variables. Trail Making Test A and B scores were natural log transformed prior to standardization. Transformed scores were also multiplied by -1 to reverse the scoring scheme. All domain scores have a mean of 0 and a SD of 1. Higher domain scores indicate greater cognitive function.

3.3.4 Statistical Analyses

Statistical analyses were performed using Stata/MP 15.1 (College Station, TX: StataCorp LLC). Descriptive statistics are presented as means ± SDs for continuous variables and percentages for categorical variables. Multiple linear regression models with bootstrapped confidence intervals (1000 replicate samples) were employed to account for potential non-normal distributions. Systolic BP, Diastolic BP, Glucose and HDL-C were examined as predictors of each cognitive domain score in three sets of analyses:

(i) Cross-sectional: W6 Cognition = W6 CV-RF + W6 covariates

(ii) Prospective: W7 Cognition = W6 CV-RF + W6 covariates

(iii) Longitudinal: W7 Cognition = W6 CV-RF + W6 covariates + W6 Cognition

Covariates were age, sex, education and ethnicity. In addition to being examined as a covariate, age was examined as a moderator of associations between each modifiable CV-RF and cognitive domain score. Longitudinal change in cognitive function was assessed using the residualized change approach, in which an outcome (e.g., Wave 7

Global Cognition) is regressed upon itself at a prior occasion (e.g., W6 Global Cognition). Further detail on the residualized change approach is provided in work by Castro-Schilo and Grimm (2018).

3.4 Results

3.4.1 Participant Characteristics

Demographic and health characteristics of study participants (n=600) at Wave 6 and Wave 7 are displayed in Table 3.1. Participants were predominantly White females. Participants were predominantly middle-aged and well educated at Wave 6. Mean systolic BP was high and mean diastolic BP, fasting glucose and HDL-C were normal. Age and diastolic BP increased and HDL-C decreased significantly between Wave 6 and Wave 7. No other significant differences in participant characteristics were observed.

Table 3.1. Participant characteristics at Wave 6 (n=600).

Variable	**Wave of the MSLS**		**P-value**
	6	**7**	
Age (years)	62.0 (11.9)	66.7 (11.8)	<0.001
Education (years)	14.7 (2.7)	14.7 (2.8)	0.342
Systolic BP (mmHg)	130.3 (21.5)	130.8 (20.4)	0.550
Diastolic BP (mmHg)	70.1 (9.8)	76.8 (9.7)	<0.001
Fasting glucose (mg/dL)	98.9 (29.0)	98.9 (26.1)	0.978
HDL-C (mg/dL)	54.3 (15.6)	52.6 (15.3)	<0.001
	Percent		
Sex (female)[a]	61.0	-	-
Race (White)[a]	93.0	-	-

[a]Did not change between Wave 6 and 7.

3.4.2 Primary Analyses

Findings of primary statistical analyses are reported in Tables 3.2 to 3.4. Standardized (β) and unstandardized (b) regression coefficients reflect the adjusted change in each cognitive domain score per 1 SD and 10 unit (mmHg or mg/dL) increase in each modifiable CV-RF, respectively. As each cognitive domain score is standardized, coefficients are reported in the z-score metric.

Table 3.2 displays the results of cross-sectional analyses examining associations between Wave 6 modifiable CV-RFs and Wave 6 cognitive function. Systolic BP was not associated with any cognitive domain in main effects models. In interaction models, systolic BP × age was negatively associated with GMS (P=0.025), VSOM (P=0.022) and ST (P=0.037). Diastolic BP was negatively associated with AR (P=0.047) in main effects models. In interaction models, diastolic BP × age was negatively associated with VSOM (P=0.009). Fasting glucose was not associated with any cognitive domain in main effects models. In interaction models, fasting glucose × age was negatively associated with Global Cognition (P=0.045) and VSOM (P=0.003). HDL-C was positively associated with Global Cognition (P=0.004), GMS (P=0.034), AR (P=0.010), VSOM (P=0.008), VC (P=0.009) and WM (P=0.005) in main effects models. In interaction models, HDL-C × age was not associated with any cognitive domain.

Table 3.3 displays the results of prospective analyses examining associations between Wave 6 modifiable CV-RFs and Wave 7 cognitive function. Systolic BP was not associated with any cognitive domain in main effects models. In interaction models, systolic BP × age was negatively associated with Global Cognition (P=0.019), GMS (P=0.036), VSOM (P=0.023) and ST (P=0.015). Diastolic BP was not associated with any cognitive domain in main effect models. In interaction models, diastolic BP × age

was negatively associated with Global Cognition (P=0.005), VSOM (P=0.009), ST (P=0.017) and WM (P=0.008). Figure 3.1 illustrates the prospective associations between age, diastolic BP and WM. Higher diastolic BP became increasingly predictive of lower prospective WM after 65 years of age. Fasting glucose and fasting glucose × age were not associated with any cognitive domain in main effects or interaction models, respectively. HDL-C was positively associated with Global Cognition (P=0.002), GMS (P=0.016), AR (P=0.017), VSOM (P=0.030), Naming (P=0.018), VC (P<0.001) and WM (P<0.001) in main effect models. Figure 3.2 illustrates the prospective association between HDL-C and WM. In interaction models, HDL-C × age was not associated with any cognitive domain.

Table 3.4 displays the results of longitudinal analyses examining associations between Wave 6 modifiable CV-RFs and residualized cognitive change between Waves 6 and 7. Systolic BP was not associated with residualized change in any cognitive domain in main effects models. In interaction models, higher systolic BP × age was associated with decline in Global Cognition (P=0.022), VEM (P=0.003) and WM (P=0.044). Diastolic BP was not associated with residualized change in any cognitive domain in main effects models. In interaction models, higher diastolic BP × age was associated with decline in Global Cognition (P=0.005), VEM (P=0.017) and WM (P=0.002). Higher fasting glucose was associated with decline in WM (P=0.032) in main effects models. In interaction models, fasting glucose × age was not associated with residualized change in any cognitive domain. Higher HDL-C was associated with gain in VC (P=0.011) and WM (P=0.041) in main effects models. In interaction models, HDL-C × age was not associated with residualized change in any cognitive domain.

Table 3.2. Results of cross-sectional analyses examining associations between Wave 6 modifiable cardiovascular risk factors and Wave 6 cognitive function.

Measure of risk	Measure	Cognitive domain								
		Global	**GMS**	**AR**	**VSOM**	**Naming**	**ST**	**VC**	**VEM**	**WM**
Systolic BP	β	-0.0015	-0.0443	-0.0609	-0.0093	0.0292	0.0268	-0.0433	-0.0025	0.0053
	b	-0.0007	-0.0205	-0.0282	-0.0043	0.0135	0.0124	-0.0201	-0.0012	0.0024
	95% LCL	-0.0300,	-0.0552,	-0.0638,	-0.0356,	-0.0177,	-0.0150,	-0.0536,	-0.0362,	-0.0342,
	95% UCL	0.0285	0.0141	0.0073	0.0269	0.0447	0.0398	0.0134	0.0339	0.0390
	P-value	0.962	0.246	0.120	0.786	0.396	0.376	0.239	0.948	0.896
Systolic BP × age	β	-0.3706	-0.7483*	-0.1460	-0.6744*	-0.1761	-0.5658*	-0.0703	0.4819	-0.1631
	b	-0.0015	-0.0031	-0.0006	-0.0028	-0.0007	-0.0023	-0.0003	0.0020	-0.0007
	95% LCL	-0.0037,	-0.0058,	-0.0031,	-0.0052,	-0.0033,	-0.0045,	-0.0029,	-0.0005,	-0.0036,
	95% UCL	0.0006	-0.0004	0.0019	-0.0004	0.0019	-0.0001	0.0024	0.0045	0.0022
	P-value	0.166	0.025	0.632	0.022	0.582	0.037	0.830	0.121	0.648
Diastolic BP	β	0.0012	-0.0454	-0.0820*	-0.0160	0.0114	0.0278	-0.0128	-0.0057	0.0284
	b	0.0012	-0.0465	-0.0840	-0.0163	0.0117	0.0284	-0.0131	-0.0059	0.0291
	95% LCL	-0.0672,	-0.1222,	-0.1669,	-0.0954,	-0.0659,	-0.0382,	-0.0817,	-0.0885,	-0.0486,
	95% UCL	0.0697	0.0293	-0.0011	0.0628	0.0893	0.0949	0.0554	0.0768	0.1068
	P-value	0.972	0.229	0.047	0.686	0.768	0.404	0.707	0.890	0.463
Diastolic BP × age	β	-0.4137	-0.3713	-0.2229	-0.7815**	-0.1318	-0.4172	-0.2008	0.3892	-0.2187
	b	-0.0039	-0.0035	-0.0021	-0.0073	-0.0012	-0.0039	-0.0019	0.0037	-0.0020
	95% LCL	-0.0085,	-0.0088,	-0.0075,	-0.0128,	-0.0084,	-0.0087,	-0.0071,	-0.0022,	-0.0078,
	95% UCL	0.0008	0.0018	0.0034	-0.0019	0.0060	0.0009	0.0033	0.0095	0.0037
	P-value	0.101	0.198	0.452	0.009	0.737	0.115	0.478	0.217	0.488
Glucose	β	-0.0420	-0.0023	-0.0246	-0.0607	-0.1083	-0.0363	-0.0119	0.0130	-0.0041
	b	-0.0145	-0.0008	-0.0085	-0.0209	-0.0373	-0.0125	-0.0041	0.0045	-0.0014
	95% LCL	-0.0447,	-0.0313,	-0.0351,	-0.0500,	-0.0874,	-0.0346,	-0.0341,	-0.0222,	-0.0320,
	95% UCL	0.0157	0.0297	0.0181	0.0081	0.0128	0.0095	0.0258	0.0312	0.0292
	P-value	0.346	0.959	0.531	0.157	0.145	0.266	0.788	0.743	0.928

Table 3.2 continued.

Glucose × age	β	-0.5567*	0.0041	-0.1078	-0.7139**	-0.8598	-0.2292	-0.2437	-0.4253	-0.2304
	b	-0.0026	0.0000	-0.0005	-0.0033	-0.0040	-0.0011	-0.0011	-0.0020	-0.0011
	95% LCL	-0.0051,	-0.0026,	-0.0028,	-0.0055,	-0.0101,	-0.0035,	-0.0038,	-0.0040,	-0.0037,
	95% UCL	-0.0001	0.0026	0.0018	-0.0011	0.0022	0.0013	0.0016	0.0001	0.0016
	P-value	0.045	0.989	0.665	0.003	0.204	0.383	0.408	0.059	0.427
HDL choles-terol	β	0.0876**	0.0808*	0.0966*	0.0898**	0.0444	0.0208	0.0868**	0.0402	0.1051**
	b	0.0560	0.0516	0.0617	0.0574	0.0283	0.0133	0.0555	0.0257	0.0672
	95% LCL	0.0177,	0.0040,	0.0145,	0.0148,	-0.0141,	-0.0318,	0.0137,	-0.0219,	0.0199,
	95% UCL	0.0943	0.0993	0.1089	0.1000	0.0707	0.0583	0.0973	0.0733	0.1145
	P-value	0.004	0.034	0.010	0.008	0.190	0.564	0.009	0.290	0.005
HDL choles-terol × age	β	0.0160	0.1270	0.3789	0.0521	-0.2844	-0.0630	0.2625	0.2482	-0.2656
	b	0.0001	0.0010	0.0030	0.0004	-0.0022	-0.0005	0.0021	0.0020	-0.0021
	95% LCL	-0.0028,	-0.0028,	-0.0005,	-0.0028,	-0.0057,	-0.0037,	-0.0014,	-0.0018,	-0.0058,
	95% UCL	0.0030	0.0048	0.0065	0.0036	0.0012	0.0028	0.0055	0.0057	0.0016
	P-value	0.932	0.605	0.090	0.801	0.200	0.764	0.237	0.302	0.262

*P<0.050; **P<0.010; ***P<0.001.

Table 3.3. Results of prospective analyses examining associations between Wave 6 modifiable cardiovascular risk factors and Wave 7 cognitive function.

Measure of risk	Measure	Cognitive domain								
		Global	**GMS**	**AR**	**VSOM**	**Naming**	**ST**	**VC**	**VEM**	**WM**
Systolic BP	β	0.0156	0.0273	-0.0082	-0.0050	0.0319	0.0382	-0.0091	0.0224	0.0070
	b	0.0072	0.0126	-0.0038	-0.0023	0.0148	0.0177	-0.0042	0.0104	0.0033
	95% LCL	-0.0198,	-0.0221,	-0.0380,	-0.0311,	-0.0133,	-0.0084,	-0.0385,	-0.0231,	-0.0321,
	95% UCL	0.0342	0.0473	0.0305	0.0265	0.0430	0.0437	0.0300	0.0438	0.0386
	P-value	0.601	0.475	0.829	0.876	0.302	0.184	0.808	0.544	0.857
Systolic BP × age	β	-0.6051*	-0.7440*	0.0556	-0.6270*	-0.3261	-0.5973*	-0.1475	-0.3548	-0.6064
	b	-0.0025	-0.0031	0.0002	-0.0026	-0.0013	-0.0025	-0.0006	-0.0015	-0.0025
	95% LCL	-0.0046,	-0.0059,	-0.0024,	-0.0048,	-0.0039,	-0.0044,	-0.0034,	-0.0041,	-0.0052,
	95% UCL	-0.0004	-0.0002	0.0029	-0.0004	0.0012	-0.0005	0.0022	0.0012	0.0002
	P-value	0.019	0.036	0.866	0.023	0.299	0.015	0.668	0.275	0.069
Diastolic BP	β	0.0047	0.0169	-0.0507	-0.0122	0.0073	0.0234	-0.0145	0.0229	0.0082
	b	0.0047	0.0174	-0.0518	-0.0124	0.0075	0.0239	-0.0149	0.0234	0.0084
	95% LCL	-0.0574,	-0.0635,	-0.1281,	-0.0844,	-0.0579,	-0.0405,	-0.0837,	-0.0471,	-0.0663,
	95% UCL	0.0669	0.0982	0.0245	0.0595	0.0729	0.0882	0.0540	0.0939	0.0831
	P-value	0.881	0.674	0.183	0.735	0.822	0.467	0.672	0.515	0.826
Diastolic BP × age	β	-0.6869**	-0.6417	0.0683	-0.7236**	-0.3857	-0.6058*	-0.4413	-0.2417	-0.8191**
	b	-0.0064	-0.0060	0.0006	-0.0068	-0.0036	-0.0057	-0.0041	-0.0023	-0.0077
	95% LCL	-0.0110,	-0.0123,	-0.0057,	-0.0119,	-0.0092,	-0.0103,	-0.0099,	-0.0074,	-0.0133,
	95% UCL	-0.0019	0.0003	0.0070	-0.0017	0.0020	-0.0010	0.0016	0.0029	-0.0020
	P-value	0.005	0.061	0.844	0.009	0.204	0.017	0.155	0.391	0.008
Glucose	β	-0.0407	0.0025	0.0085	-0.0469	-0.0814	-0.0550	0.0046	0.0385	-0.0567
	b	-0.0140	0.0008	0.0029	-0.0162	-0.0281	-0.0190	0.0016	0.0133	-0.0195
	95% LCL	-0.0419,	-0.0244,	-0.0281,	-0.0435,	-0.0659,	-0.0426,	-0.0262,	-0.0103,	-0.0522,
	95% UCL	0.0138	0.0261	0.0339	0.0112	0.0098	0.0046	0.0293	0.0368	0.0131
	P-value	0.323	0.948	0.854	0.247	0.146	0.115	0.912	0.269	0.241

Table 3.3 continued.

Glucose × age	β	-0.4435	-0.2602	-0.2238	-0.5107	-0.6142	-0.2348	-0.3631	-0.2662	-0.3067
	b	-0.0021	-0.0012	-0.0010	-0.0024	-0.0029	-0.0011	-0.0017	-0.0012	-0.0014
	95% LCL	-0.0046,	-0.0035,	-0.0041,	-0.0050,	-0.0069,	-0.0034,	-0.0043,	-0.0033,	-0.0042,
	95% UCL	0.0005	0.0010	0.0021	0.0002	0.0012	0.0012	0.0009	0.0008	0.0013
	P-value	0.109	0.294	0.512	0.074	0.163	0.345	0.202	0.236	0.309
HDL choles-terol	β	0.0978**	0.0851*	0.0862*	0.0745*	0.0744*	0.0419	0.1248***	0.0584	0.1326**
	b	0.0625	0.0544	0.0551	0.0476	0.0475	0.0268	0.0798	0.0373	0.0847
	95% LCL	0.0236,	0.0103,	0.0097,	0.0046,	0.0082,	-0.0146,	0.0385,	-0.0084,	0.0362,
	95% UCL	0.1013	0.0985	0.1006	0.0906	0.0868	0.0682	0.1210	0.0830	0.1333
	P-value	0.002	0.016	0.017	0.030	0.018	0.205	<0.001	0.109	0.001
HDL choles-terol × age	β	-0.0849	-0.2168	0.3893	-0.1365	-0.0183	-0.2344	0.1849	0.0560	-0.1074
	b	-0.0007	-0.0017	0.0031	-0.0011	-0.0001	-0.0019	0.0015	0.0004	-0.0008
	95% LCL	-0.0037,	-0.0051,	-0.0007,	-0.0045,	-0.0036,	-0.0049,	-0.0020,	-0.0030,	-0.0043,
	95% UCL	0.0024	0.0017	0.0068	0.0024	0.0033	0.0012	0.0049	0.0039	0.0026
	P-value	0.667	0.320	0.110	0.540	0.934	0.232	0.405	0.803	0.634

*P<0.050; **P<0.010; ***P<0.001.

Table 3.4. Results of longitudinal analyses examining associations between Wave 6 modifiable cardiovascular risk factors and residualized cognitive change between Waves 6 and 7.

Measure of risk	**Measure**	**Cognitive domain**								
		Global	**GMS**	**AR**	**VSOM**	**Naming**	**ST**	**VC**	**VEM**	**WM**
Systolic BP	β	0.0169	0.0484	0.0291	0.0022	0.0130	0.0179	0.0268	0.0241	0.0030
	b	0.0078	0.0225	0.0135	0.0010	0.0049	0.0083	0.0124	0.0111	0.0014
	95% LCL	-0.0052,	-0.0082,	-0.0131,	-0.0162,	-0.0123,	-0.0081,	-0.0047,	-0.0125,	-0.0210,
	95% UCL	0.0209	0.0532	0.0401	0.0182	0.0221	0.0247	0.0295	0.0347	0.0238
	P-value	0.241	0.151	0.321	0.906	0.575	0.322	0.154	0.355	0.903
Systolic BP × age	β	-0.2914*	-0.3960	0.1458	-0.1085	-0.4847	-0.1699	-0.0891	-0.6744**	-0.4819*
	b	-0.0012	-0.0016	0.0006	-0.0004	-0.0016	-0.0007	-0.0004	-0.0028	-0.0020
	95% LCL	-0.0022,	-0.0040,	-0.0015,	-0.0019,	-0.0034,	-0.0019,	-0.0020,	-0.0046,	-0.0039,
	95% UCL	-0.0002	0.0008	0.0027	0.0010	0.0002	0.0005	0.0013	-0.0010	-0.0001
	P-value	0.022	0.182	0.583	0.538	0.074	0.263	0.657	0.003	0.044
Diastolic BP	β	0.0036	0.0383	-0.0005	0.0001	-0.0081	0.0023	-0.0039	0.0267	-0.0135
	b	0.0037	0.0392	-0.0005	0.0001	-0.0068	0.0024	-0.0040	0.0273	-0.0138
	95% LCL	-0.0260,	-0.0306,	-0.0563,	-0.0367,	-0.0466,	-0.0353,	-0.0468,	-0.0269,	-0.0625,
	95% UCL	0.0333	0.1090	0.0552	0.0369	0.0331	0.0400	0.0388	0.0815	0.0349
	P-value	0.807	0.271	0.985	0.995	0.740	0.903	0.855	0.324	0.578
Diastolic BP × age	β	-0.3372**	-0.4690	0.2043	-0.1233	-0.4453	-0.2908	-0.2751	-0.4994*	-0.6524**
	b	-0.0032	-0.0044	0.0019	-0.0012	-0.0034	-0.0027	-0.0026	-0.0047	-0.0061
	95% LCL	-0.0053,	-0.0101,	-0.0034,	-0.0039,	-0.0069,	-0.0059,	-0.0063,	-0.0085,	-0.0099,
	95% UCL	-0.0010	0.0013	0.0072	0.0016	0.0001	0.0004	0.0012	-0.0009	-0.0023
	P-value	0.005	0.130	0.479	0.414	0.057	0.092	0.177	0.017	0.002
Glucose	β	-0.0051	0.0035	0.0235	-0.0001	0.0106	-0.0275	0.0145	0.0300	-0.0536*
	b	-0.0017	0.0012	0.0081	0.0000	0.0030	-0.0095	0.0050	0.0103	-0.0185
	95% LCL	-0.0109,	-0.0186,	-0.0158,	-0.0146,	-0.0095,	-0.0221,	-0.0087,	-0.0059,	-0.0353, -
	95% UCL	0.0074	0.0210	0.0319	0.0145	0.0155	0.0031	0.0187	0.0266	0.0016
	P-value	0.710	0.905	0.507	0.995	0.638	0.141	0.476	0.211	0.032

Table 3.4 continued.

Glucose × age	β	0.0294	-0.2626	-0.1586	0.0399	-0.1431	-0.0614	-0.1613	0.0128	-0.1308
	b	0.0001	-0.0012	-0.0007	0.0002	-0.0005	-0.0003	-0.0007	0.0001	-0.0006
	95% LCL	-0.0007,	-0.0031,	-0.0032,	-0.0011,	-0.0019,	-0.0013,	-0.0018,	-0.0014,	-0.0022,
	95% UCL	0.0010	0.0006	0.0017	0.0015	0.0008	0.0008	0.0003	0.0015	0.0009
	P-value	0.748	0.200	0.555	0.777	0.436	0.590	0.181	0.937	0.444
HDL cholesterol	β	0.0236	0.0478	0.0283	0.0054	0.0178	0.0262	0.0533*	0.0321	0.0528*
	b	0.0151	0.0305	0.0181	0.0034	0.0093	0.0167	0.0341	0.0205	0.0337
	95% LCL	-0.0028,	-0.0098,	-0.0165,	-0.0228,	-0.0121,	-0.0053,	0.0078,	-0.0100,	0.0013,
	95% UCL	0.0329	0.0709	0.0527	0.0297	0.0307	0.0388	0.0603	0.0510	0.0662
	P-value	0.097	0.138	0.305	0.797	0.394	0.137	0.011	0.188	0.041
HDL cholesterol × age	β	-0.0984	-0.2753	0.1631	-0.1766	0.1152	-0.1867	-0.0312	-0.1068	0.0944
	b	-0.0008	-0.0022	0.0013	-0.0014	0.0007	-0.0015	-0.0002	-0.0008	0.0007
	95% LCL	-0.0023,	-0.0054,	-0.0016,	-0.0034,	-0.0015,	-0.0033,	-0.0025,	-0.0033,	-0.0017,
	95% UCL	0.0008	0.0011	0.0042	0.0006	0.0030	0.0004	0.0020	0.0016	0.0032
	P-value	0.321	0.189	0.388	0.179	0.516	0.114	0.830	0.503	0.555

*P<0.050; **P<0.010; ***P<0.001.

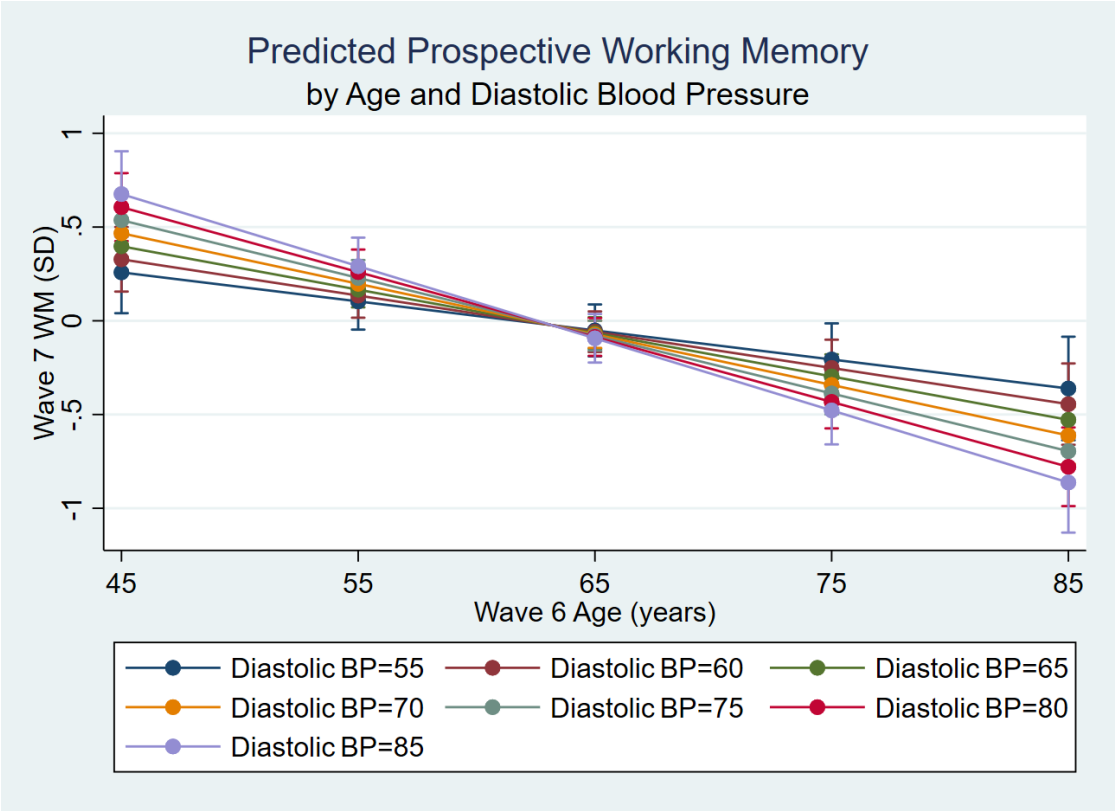

Figure 3.1. Age and diastolic blood pressure as predictors of Working Memory in prospective analyses.

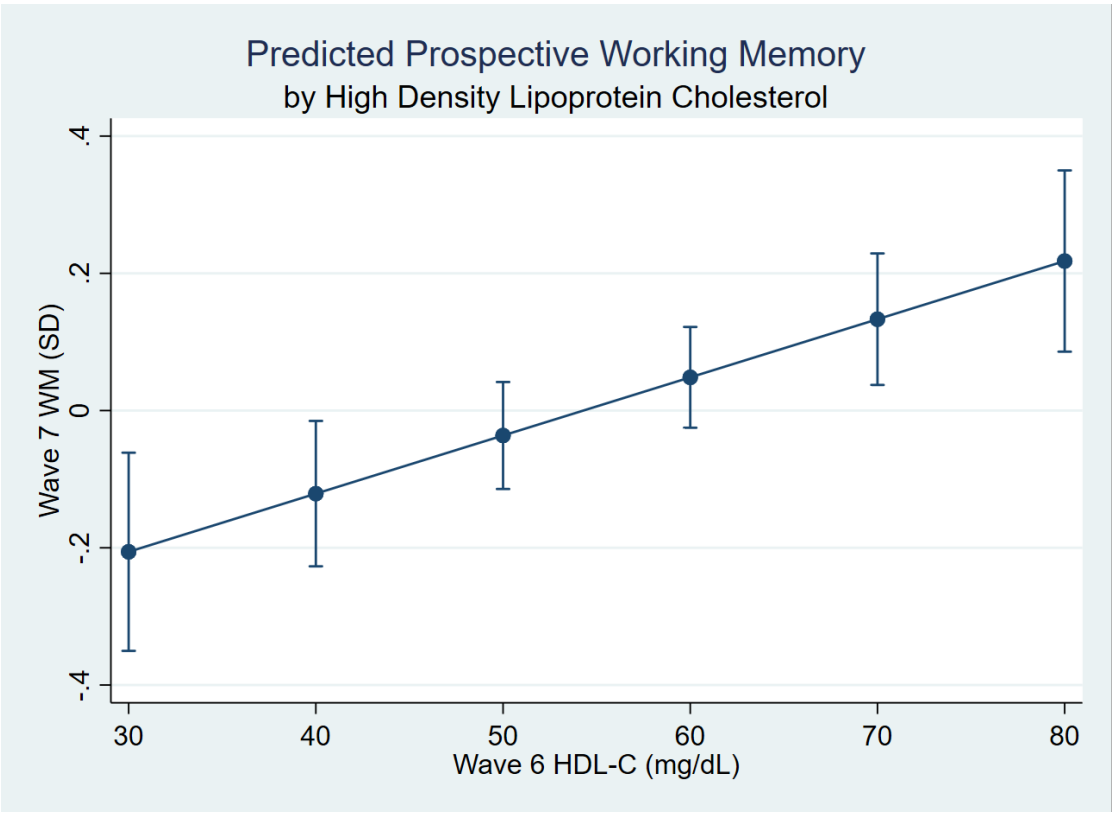

Figure 3.2. High density lipoprotein cholesterol as a predictor of Working Memory in prospective analyses.

3.4.3 Sensitivity Analyses

Mean systolic BP based on all 15 measures was 130.3 ± 21.5 mmHg and mean systolic BP based on the 5 seated measures was 132.2 ± 22.2 mmHg. The variables were correlated at r=.97. Findings were essentially identical for each variable. However, the negative cross-sectional association between systolic BP × age and VSOM became marginally significant (P=0.067) and the negative prospective association between systolic BP × age and WM became significant (P=0.029) when systolic BP based on all 15 measures was replaced with systolic BP based on the 5 seated measures.

Mean diastolic BP based on all 15 measures was 70.1 ± 9.8 mmHg and mean diastolic BP based on the 5 seated measures was 70.8 ± 10.2 mmHg. The variables were correlated at r=.96. Findings were essentially identical for each variable. However, the negative cross-sectional association between diastolic BP and AR became marginally significant (P=0.065), the negative prospective association between diastolic BP × age and GMS became significant (P=0.014) and the negative longitudinal association between diastolic BP × age and GMS became significant (P=0.040) when diastolic BP based on all 15 measures was replaced with diastolic BP based on the 5 seated measures.

3.5 Discussion

Research studies examining the role of modifiable CV-RFs in the nonnormative cognitive aging trajectory have reported inconsistent findings to date. We have attempted to clarify the literature by providing a comprehensive examination of cross-sectional, prospective and longitudinal associations between modifiable CV-RFs and cognitive function in this research. Systolic BP, diastolic BP and fasting glucose were negatively and HDL-C was positively associated with several cognitive domains. Some

associations were observed using the entire sample of MSLS participants, while others were significant only in the context of advancing age.

Hypertension (BP ≥140/90 mmHg) has been associated with cerebral microbleeds (Shams, et al., 2015), lacunar infarcts (Bezerra, et al., 2012) and white matter hyperintensities (Verhaaren, et al., 2013; Raz, Rodrigue, Kennedy, & Acker, 2007). Hypertension has also been associated with lower cognitive function (Elias, Goodell, & Dore, 2012), albeit findings for its components have been mixed. Some previous studies report an inverse association between BP and cognitive function (Elias P. K., Elias, Robbins, & Budge, 2004; Elias, Wolf, D'Agostino, Cobb, & White, 1993), while others report no association (Molander, Gustafson, & Lovheim, 2010), a J-shaped association (Paran, Anson, & Reuveni, 2003) or a U-shaped association (Glynn, et al., 1999; Waldstein, Giggey, Thayer, & Zonderman, 2005). Systolic and diastolic BP were negatively associated with several domains of cognitive function in this research. In cross-sectional analyses we found that each 1 SD of higher systolic BP (22 mmHg) × age (12 years) was associated with 0.57-0.75 SD lower GMS, VSOM and ST, each 1 SD of higher diastolic BP (10 mmHg) was associated with 0.08 lower AR and each 1 SD of higher diastolic BP × age was associated with 0.78 SD lower VSOM. In prospective analyses we found that each 1 SD of higher systolic BP × age was associated with 0.60-0.74 SD lower Global Cognition, GMS, VSOM and ST and each 1 SD of higher diastolic BP × age was associated with 0.61-0.82 SD lower Global Cognition, GMS, VSOM and ST. Lastly, in longitudinal analyses we found that each 1 SD of higher systolic BP × age was associated with 0.29-0.67 SD decline in Global Cognition, VEM and WM and each 1 SD of higher diastolic BP × age was associated with 0.34-0.65 SD decline in Global Cognition, VEM and WM.

Diabetes mellitus (fasting glucose ≥126 mg/dL) has been associated with cerebral amyloidosis, microvascular disease and lower cognitive function, nearly doubling an individual's lifetime risk for dementia. (Luchsinger, et al., 2007; Biessels, Strachan, Visseren, Kappelle, & Whitmer, 2014; Cheng, Huang, Deng, & Wang, 2012) Interventions targeting adults at risk for diabetes could potentially slow nonnormative cognitive aging. However, the full range of fasting glucose is rarely examined as a predictor of cognitive function and results of existing studies are inconsistent. (Dybjer, Nilsson, Engström, Helmer, & Nägga, 2018) Some report a linear association between fasting glucose and cognitive function in all adults (Dybjer, Nilsson, Engström, Helmer, & Nägga, 2018; Cukierman-Yaffe, et al., 2009), while others report an association only in adults with known diabetes (Tuligenga, et al., 2014). Fasting glucose was negatively associated with several domains of cognitive function in this research. In cross-sectional analyses we found that each 1 SD of higher fasting glucose (29 mg/dL) × age was associated with 0.56 SD lower Global Cognition and 0.71 SD lower VSOM. No significant associations were observed in prospective analyses and in longitudinal analyses we found that each 1 SD of higher fasting glucose was associated with 0.05 SD lower WM.

Nearly one-fourth of all cholesterol in the body can be found within the brain, where it is vital for maintaining brain structure and function. (Reed, et al., 2014; Reiss, et al., 2004) Adequate levels of HDL-C are crucial for synapse maturation, maintenance of synaptic plasticity and the prevention of β-amyloid plaque formation. (Michikawa, 2003; Olesen, 2000) Previous studies have identified HDL-C as a stronger predictor of cognitive function than other forms of cholesterol. (He, et al., 2016; Reitz, et al., 2010) However, findings of associations between HDL-C and cognitive function are not reported universally. (Svensson, et al., 2019; Ma, et al., 2017; Corley, Starr, & Deary,

2015) HDL-C was positively associated with several domains of cognitive function in this research, irrespective of age. In cross-sectional analyses, each 1 SD of higher HDL-C (16 mg/dL) was associated with 0.08-0.11 SD higher Global Cognition, GMS, AR, VSOM, VC and WM. In prospective analyses, each 1 SD of higher HDL-C was associated with 0.07-0.13 SD higher Global Cognition, GMS, AR, VSOM, Naming, VC and WM. Lastly, in longitudinal analyses each 1 SD of higher HDL-C was associated with 0.05 SD higher VC and WM.

Each modifiable CV-RF examined in this research is treatable. Guidelines for the treatment of hypertension involve lowering BP to <120/80 mmHg using a combination of lifestyle changes and antihypertensive medications (Whelton, et al., 2018). Guidelines for the treatment of diabetes involve maintaining a fasting glucose level between 80-130 mg/dL using a combination of lifestyle changes and antidiabetic medications (American Diabetes Association, 2018). Lastly, guidelines for the treatment of dyslipidemia involve raising HDL-C to >40 mg/dL using lifestyle changes and, in certain cases, medications that lower LDL cholesterol and triglycerides. (Jellinger, et al., 2017) We found that higher systolic BP, diastolic BP and fasting glucose become strong predictors of lower cognitive function with advancing age. Efforts to monitor and treat these modifiable CV-RFs thus become increasingly important as individuals move through adulthood. HDL-C was a strong predictor of cognitive function at all ages and should be strictly monitored and treated accordingly.

Additional research is needed to confirm our findings and develop interventions to slow nonnormative cognitive aging. Effect sizes reported in this research are small. Short-term effects resulting from the treatment of modifiable CV-RFs based on current guidelines would be limited for adults in primary care settings. However, nonnormative

cognitive aging is progressive and small reductions in risk resulting from early treatment could have significant long-term implications at the population level. While additional research is conducted, physicians should educate their patients on the importance of maintaining CV health for promoting enhanced brain aging. (Qui, 2015)

3.5.1 Study Limitations

The pathophysiological mechanisms linking certain modifiable CV-RFs and cognitive function are not fully understood in the literature. The MSLS did not include brain imaging, which would have allowed us to conduct an in-depth examination of these mechanisms. Attrition between Wave 6 and Wave 7 was high and the use of longitudinal data resulted in the loss of a substantial number of participants. However, attrition patterns were evaluated and did not substantially alter the results of this research. The longitudinal findings observed in this research were limited, which could be the result of the short follow-up period between Wave 6 and Wave 7. Results of this research are likely conservative, as MSLS participants were well educated and education protects against decline by increasing cognitive reserve. (Meng & D'Arcy, 2012)

3.5.2 Study Strengths

The design of the MSLS permitted us to examine cross-sectional, prospective and longitudinal associations between major modifiable CV-RFs and cognitive function in a community-dwelling sample of adults who not selected for CVD or cognitive impairment. Several major modifiable CV-RFs and an extensive neuropsychological test battery indexing multiple cognitive domains were included. Associations were examined across adulthood using a three commonly employed study designs. To our

knowledge, this is one of most comprehensive examinations of major modifiable CV-RFs and cognitive function in the literature to date.

3.6 Conclusion

Significant cross-sectional, prospective and longitudinal associations between modifiable CV-RFs and cognitive function were observed. Systolic BP, diastolic BP and fasting glucose were negatively associated with cognitive function and HDL-C was positively associated with cognitive function. While some associations were observed for all participants, others were moderated by advancing age. Additional research is needed to confirm these findings as well as explore the pathophysiological mechanisms underlying each association. Such research will allow us to determine how best to intervene in order to slow nonnormative cognitive aging in future interventions.

Chapter 4

ARTERIAL STIFFNESS DIFFERENTIALLY MEDIATES ASSOCIATIONS BETWEEN AGGREGATE MODIFIABLE CARDIOVASCULAR RISK AND COGNITIVE FUNCTION AMONG CARRIERS AND NONCARRIERS OF THE APOLIPOPROTEIN E ε4 ALLELE

4.1 Abstract

Background: Nonnormative cognitive aging is characterized by progressive cognitive decline and is a major contributor to global disability burden. Modifiable CV-RFs aggregate to increase risk for nonnormative cognitive aging through arterial stiffening, which is a promising intervention target. This research provides an in-depth examination of arterial stiffness as a mediator of associations between modifiable CV risk and cognitive function in adults with variable genetic risk.

Methods: Participants were community-dwelling adults from the MSLS (n=577; M_{Age} 66.3±11.8 years; 61% female). Linear regression was used to relate 6 measures of modifiable CV risk to 9 cognitive domains. Systolic BP, diastolic BP, fasting glucose and HDL-C were examined as modifiable CV-RFs. FRS and MSLS-CVRFS were examined as measures of aggregate CV risk. Pulse wave velocity (PWV) was used to assess arterial stiffness and was examined as a mediator of each association using path analysis. All analyses were performed in carriers and noncarriers of the ApoE ε4 allele and path differences were compared using Wald χ^2 tests.

Results: Mediation analyses were significant for ApoE ε4 carriers, but not noncarriers. Through higher PWV: 1. Higher systolic BP was associated with lower cognitive in 6 domains; 2. Higher fasting glucose was associated with lower cognitive in 4

domains; 3. Higher HDL-C was associated with higher function in 1 domain, and; 4. Higher FRS was associated with lower cognitive in 4 domains.

Conclusion: Arterial stiffness mediated associations between modifiable CV risk and cognitive function in ApoE ε4 carriers. Arterial stiffness was the strongest mediator of associations between systolic BP, FRS, fasting glucose and cognitive function. Further research is needed to confirm these findings and develop interventions to slow nonnormative cognitive aging.

4.2 Introduction

Complex cognitive changes accompany aging and it will become increasingly important to understand them as the number of adults over 65 years of age increases from 617M in 2015 to 1.6B in 2050. (He, Goodkind, & Kowal, 2016) Normative cognitive aging is characterized by subtle, but unavoidable cognitive decline that does not interfere with activities of daily living. (Harada, Love, & Triebel, 2013) Nonnormative cognitive aging is characterized by accelerated cognitive decline caused by disease that results in severe disability. The hallmark of nonnormative cognitive aging is dementia, a terminal syndrome that affects 47M people globally and costs >$1T per year. (Wimo, et al., 2017) Pervasive cognitive decline begins up to 30 years before the emergence of clinical symptoms in the trajectory (see Figure 1.1) and an intervention slowing decline could prevent up to 57% of the 131M dementia cases expected by 2050. (Alzheimer's Association, 2017; Singh-Manoux & Kivimaki, 2010) RF modification early in the nonnormative cognitive aging trajectory is our best hope for accomplishing this goal. However, no standard, evidence-based interventions currently exist.

The arteries are responsible for delivering oxygenated blood to systemic body tissue. (Hall, 2015) Arterial stiffening is an age-related process accelerated by high

modifiable CV risk, including the presence of individual modifiable CV-RFs and their aggregation. (Mitchell, 2008) Blood flow patterns are altered and damage to the heart, brain and other vital high-flow organs is incurred as the arteries stiffen, especially among carriers of the ApoE ε4 allele. (Lui, Kanekiyo, Xu, & Bu, 2013) CVD and dementia are common outcomes (Mitchell, 2008), with high modifiable CV risk and subsequent arterial stiffness accounting for up to 90% of the >423M CVD cases existing today (Roth, et al., 2017).

Interventions targeting modifiable CV risk are frequently implemented in primary care settings to prevent CVD (World Health Organization, 2016) and, as a byproduct, dementia (Tariq & Barber, 2018). Arterial stiffness is also fairly easy and inexpensive to assess (Singer, Trollor, Baune, Sachdev, & Smith, 2014) and therapeutic strategies have been proposed to modulate stiffening processes (Janić, Lunder, & Sabovič, 2014). With such strategies available, arterial stiffness could be an additional target for interventions designed to slow nonnormative cognitive aging and delay or prevent dementia, especially in carriers of the ApoE ε4 allele. However, the precise role of arterial stiffness in associations between modifiable CV risk and cognitive function is unclear and a stronger evidence base is needed before effective interventions can be developed and implemented.

The purpose of this research was to examine arterial stiffness as a mediator of associations between modifiable CV risk and cognitive function in carriers and noncarriers of the ApoE ε4 allele. Systolic BP, diastolic BP, fasting glucose and HDL-C were examined as modifiable CV-RFs and FRS and MSLS-CVRFS were examined as measures of aggregate CV risk. We hypothesized that higher arterial stiffness would mediate associations between higher modifiable CV risk and lower cognitive function

and that the mediating role of arterial stiffness would be strongest among ApoE ε4 carriers.

4.3 Methods

4.3.1 Study Design

Data for this research came from the MSLS, a 35-year study of aging, CV risk and cognitive function. Participants were community-dwelling adult residents of Central New York at the time of recruitment. Initial exclusion criteria were inability to comprehend English, alcoholism and diagnosed psychiatric illness. Participants for this research underwent ApoE genotyping at Wave 6 (2001-2006) and completed comprehensive neuropsychological and CV assessment at Wave 7 (2006-2010).

Wave 6 of the MSLS included 1084 individuals. Those who moved out of state (n=137) were not invited to participate in Wave 7 due to funding changes and an additional 184 were lost to follow-up. Attrition was associated with lower cognitive function, higher aggregate CV risk and Black or other non-White race. Results of this research were not substantially influenced by attrition. Exclusions for this research were made based on: (i) missing ApoE genotype data at Wave 6 (n=50); (ii) missing cognitive data at Wave 7 (n=88); (iii) Parkinson's disease diagnosis at Wave 7 (n=4); (iv) dementia diagnosis at Wave 7 (n=11); (v) Stroke diagnosis at Wave 7 (n=31), and; (vi) active dialysis treatment at Wave 7 (n=2). The final sample included 577 participants.

Participants undergoing dialysis and those with history of stroke, Parkinson's disease or dementia were excluded due to our interested in examining associations between modifiable CV risk and cognitive function in those without severe impairment. Dementia diagnosis was determined by a geriatric physician, social psychologist and two neuropsychologists using neuropsychological data, medical records and the

National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria. (McKhann, et al., 1984) Diagnostic decisions have been confirmed using guidelines from the International Classification of Diseases, 10th Edition. (World Health Organization, 1992) Stroke was defined as a focal neurological deficit of acute onset persisting for more than 24 hours. Stroke and Parkinson's disease were self-reported and confirmed by medical history review.

The MSLS study protocol was developed in accordance with declaration of Helsinki guidelines and approved by the University of Maine Institutional Review Board. Informed consent was obtained from all study participants prior to data collection.

4.3.2 Study Procedures

Participants self-reported their demographic, socioeconomic and lifestyle characteristics using the Nutrition and Health Questionnaire (Riboli & Kaaks, 1997) one week prior to laboratory testing. Laboratory testing began at 9:00 AM following an overnight fast. Blood samples were collected upon arrival. A 15-minute supine rest was followed by automated BP assessment and pulse wave analysis. A light breakfast was followed by a physical examination with medical history review and neuropsychological assessment. Participants were mailed a summary of their examination results one week later with a request that they review their report with a physician.

The Nutrition and Health Questionnaire was used to report smoking status (never, current or former). History of CVD (coronary artery disease, angina pectoris, myocardial infarction, heart failure or transient ischemic attack) was self-reported and confirmed by medical history review. tHcy (μmol/L) and TC, HDL-C, LDL-C, triglyceride, creatinine and glucose (all mg/dL) were obtained from a fasting blood sample

using standard assay methods detailed by Elias et al. (2006). Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dL or self-reported treatment with antidiabetic medication. eGFR (mL/min/1.73m^2) was calculated using the CKD Epidemiology Collaboration equation. (Levey, et al., 2009) Standard polymerase chain reaction and restriction enzyme digest with HhaI was used to determine Apoe genotype (0 vs 1-2 ε4 alleles). (Hixson & Vernier, 1990) Systolic and diastolic BP (both mmHg) assessment was automated (GE Critikon Dinamap Pro Care, oscillometric method) and consisted of 5 measurements each taken in the seated, recumbent and standing positions. Hypertension was defined as averaged BP ≥140/90 mmHg or self-reported treatment with antihypertensive medication. The SphygmoCor system (AtCor Medical) was used to assess PWV (m/s), the gold-standard measure of arterial stiffness which reflects the time taken for the arterial pulse wave to travel from the carotid to the femoral artery. (Crichton, Elias, & Robbins, 2014) Height (m) and weight (kg) were obtained by an examiner and used to calculate BMI (kg/m^2).

4.3.3 Aggregate Cardiovascular Risk Scores

Modified versions of the FRS and MSLS-CVRFS were used to index aggregate CV risk. Each measure is point-based and calculated using modifiable CV-RFs. Scoring schemes are described briefly below. Additional information can be found in Table 2.1 and Table 2.2.

The FRS is the most widely adopted screening tool for 10-year CVD risk in research and primary care settings worldwide. (Dhingra & Vasan, 2012) Calculation of the FRS is based on: age (years), systolic BP (mmHg), antihypertensive medication use (yes vs no), TC (mg/dL), HDL-C (mg/dL), smoking status (smoker vs nonsmoker) and diabetes mellitus (present vs absent). Formulas are sex-specific and can be found in

work by D'Agostino et al. (2008). Inclusion of age in the FRS is controversial and has been shown to reduce accuracy of aggregate CV risk prediction. Young adults with high modifiable risk have low short-term but high lifetime risk estimates, leading to under-treatment and missed opportunity for early intervention. (Leening, Cook, & Ridker, 2017) Moreover, short-term risk in older adults is overestimated due to competing causes of death, leading to overtreatment, emotional stress and financial burden. (Dhingra & Vasan, 2012) Taking these considerations into account, age was removed from FRS calculation in this research.

The MSLS-CVRFS is a screening tool for 5-year MCI risk based on an individual's current CV health. (Sullivan, 2017) Calculation of the MSLS-CVRFS is based on: hypertension (present vs absent), diabetes mellitus (present vs absent), history of CVD (yes vs no), obesity (BMI ≥30 vs <30), ApoE genotype (1-2 vs 0 ε4 alleles), smoking status (smoker vs nonsmoker), low HDL-C (<40 vs ≥40 mg/dL), high LDL cholesterol (>160 vs ≤160 mg/dL), high triglycerides (>200 vs ≤200 mg/dL), high tHcy (>13 vs ≤13 μmol/L), high CRP (>3 vs ≤3 mg/L) and low eGFR (<60 vs ≥60 mL/min/1.73m^2). ApoE genotype was removed from MSLS-CVRFS calculation in this research because it was examined as a moderator. CRP was not assessed at Wave 7 of the MSLS and was also removed.

4.3.4 Cognitive Domain Scores

The MSLS neuropsychological test battery includes 21 established tests and subscales, which are used to index an array of cognitive abilities (Table 2.3). Several of these have been combined by Elias et al. (2009) via factor analysis to produce four cognitive domains: VEM, ST, WM and VSOM. The Similarities Test was also considered by Elias et al. (2009) and was found to load on multiple factors. It is thus included as an

individual test indexing AR. This research also includes other individual tests indexing Naming, VC and GMS, as well as a domain of Global Cognition created using every test except for the Mini-Mental State Examination. Cognitive domain scores should be created using at least two tests in practice. (Elias, Torres, & Davey, 2018) This research included several domains indexed by a single test to make use of the full MSLS neuro-psychological test battery.

Cognitive domain scores were created by: (i) standardizing raw test scores; (ii) averaging the scores of tests used to define each domain, and; (iii) re-standardizing the averaged variables. Trail Making Test A and B scores were natural log transformed prior to standardization. Transformed scores were also multiplied by -1 to reverse the scoring scheme. All domain scores have a mean of 0 and a SD of 1. Higher domain scores indicate greater cognitive function.

4.3.5 Statistical Analyses

Statistical analyses were performed using STATA/MP 15.1 (College Station, TX: StataCorp LLC). Descriptive statistics are presented as means ± SDs for continuous variables and percentages for categorical variables. Arterial stiffness was examined as a mediator of cross-sectional associations between modifiable CV risk and cognitive function in carriers and noncarriers of the ApoE ε4 allele. A conceptual model of the mediation pathway is displayed in Figure 4.1.

Arterial stiffness was indexed using PWV. Modifiable CV risk was indexed using: 1. major modifiable CV-RFs: systolic BP, diastolic BP, fasting glucose and HDL-C, and; 2. measures of aggregate CV risk: FRS and MSLS-CVRFS. Cognitive function was indexed using Global Cognition, GMS, AR, VSOM, Naming, ST, VC, VEM and

WM scores. Covariates were age, sex, education and race. Analyses were performed in carriers and noncarriers of the ApoE ε4 allele.

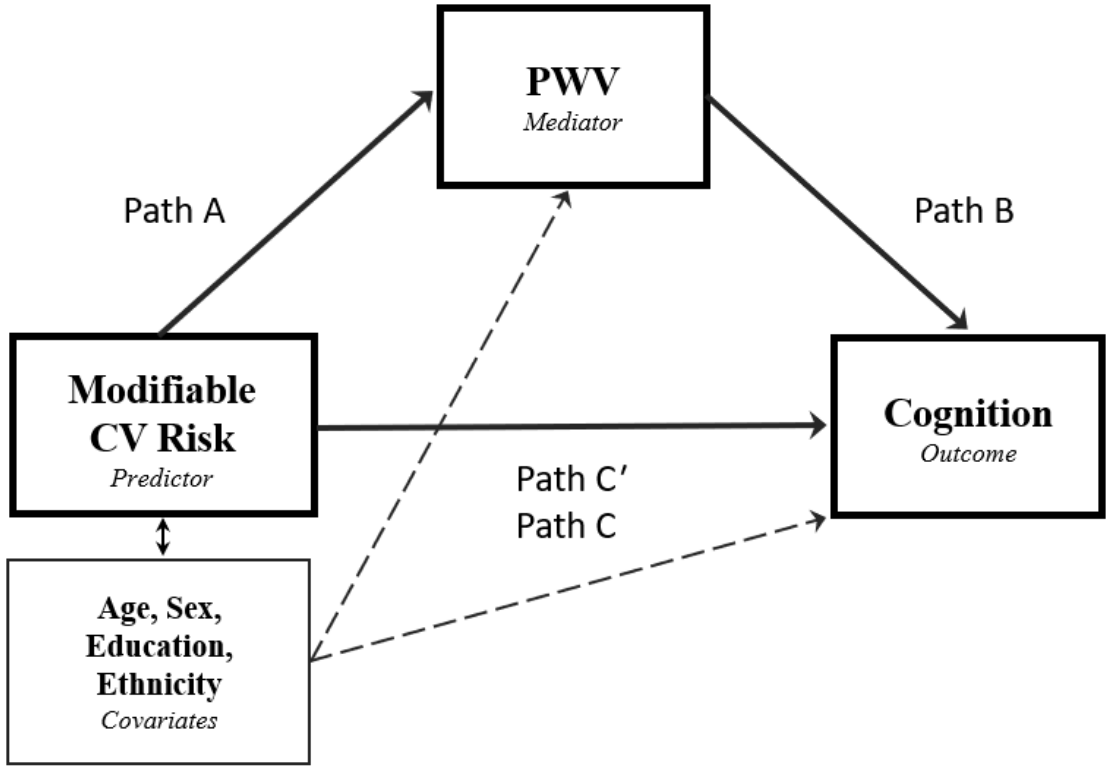

Figure 4.1. Mediation analysis conceptual model.

Multiple linear regression models with bootstrapped confidence intervals (1000 replicate samples) were used to obtain total effects (path C: A*B+C′). Maximum likelihood estimation path analysis models with bootstrapped confidence intervals (1000 replicate samples) were used to obtain direct (path C′) and indirect effects (paths A and B). Traditionally, mediation occurs when the total and indirect effects are significant and

the direct effect is nonsignificant or reduced in absolute size. (Baron & Kenny, 1986; James & Brett, 1984; Judd & Kenny, 1981) Most contemporary analyses agree that mediation occurs when indirect effects are significant, regardless of total and direct effects. (Hayes, 2009; Shrout & Bolger, 2002) Differences in mediation between ApoE ε4 carriers and non-carriers were evaluated using Wald χ^2 tests.

4.4 Results

4.4.1 Participant Characteristics

Demographic and health characteristics of study participants (n=577) at Wave 7 are displayed in Table 4.1 by ApoE genotype. Participants were predominantly White females and approximately 29% were carriers of the ApoE ε4 allele. No significant differences in characteristics were observed between carriers and noncarriers.

Participants were predominantly elderly (M_{age} 66.3±11.8 years) and well educated. Mean systolic BP was high and TC was borderline high. Mean eGFR was indicative of Stage 2 CKD and BMI of overweight status. Mean diastolic BP, fasting glucose, LDL-C, HDL-C, triglyceride and tHcy levels were normal. FRS (range: -5 to 12) and MSLS-CVRFS (range: 0 to 7) were indicative of low to moderate aggregate CV risk. The majority of participants did not have CVD or diabetes, had hypertension, were receiving antihypertensive treatment and were not smokers.

Table 4.1. Participant characteristics at Wave 7 (n=577).

Variable	ApoE ε4 carrier		
	No (n=410)	**Yes (n=167)**	**P-value**
Age (years)	66.8 (11.6)	65.1 (12.1)	0.112
Education (years)	14.7 (2.7)	14.7 (2.9)	0.821
Systolic BP (mmHg)	130.7 (20.0)	130.4 (21.2)	0.851
Diastolic BP (mmHg)	76.9 (9.7)	76.7 (9.7)	0.778
Fasting glucose (mg/dL)	98.2 (23.5)	98.9 (28.1)	0.763
TC (mg/dL)	187.0 (39.0)	188.6 (41.6)	0.665
LDL-C (mg/dL)	111.1 (32.3)	113.5 (34.2)	0.432
HDL-C (mg/dL)	53.3 (14.9)	51.2 (16.5)	0.138
Triglycerides (mg/dL)	113.1 (65.1)	126.0 (99.3)	0.066
PWV (m/s)	10.7 (3.0)	10.7 (3.3)	0.998
eGFR (mL/min/1.73m^2)	65.2 (14.7)	67.2 (16.8)	0.152
tHcy (μmol/L)	10.4 (3.2)	10.5 (4.0)	0.654
BMI (kg/m^2)	29.8 (6.5)	29.8 (7.4)	0.982
FRS (points)	3.1 (3.7)	3.6 (4.0)	0.140
MSLS-CVRFS (points)	2.2 (1.5)	2.4 (1.7)	0.197
	Percent		
Sex (female)	61.0	62.0	0.919
Race (White)	94.0	92.0	0.267
CVD (yes)	14.0	19.0	0.132
Diabetic (yes)	15.0	17.0	0.410
Hypertensive (yes)	64.0	67.0	0.505
Treated for high BP (yes)	58.0	59.0	0.846
Smoker (yes)	8.0	9.0	0.554

4.4.2 Mediation Analyses

Tables 4.2 to 4.10 display the results of multiple linear regression, path analyses and Wald χ^2 tests. Standardized regression coefficients (β; risk unit: 1 SD) and unstandardized regression coefficients (b; risk unit: 1 mmHg, mg/dL, point or m/s) are presented for each analysis. Coefficients for the total (path C) and direct (path C′) effects reflect the adjusted change in cognitive domain score per unit increase in each measure of modifiable CV risk. Coefficients for the indirect effects (paths A and B) reflect the adjusted change in PWV and cognitive domain score per unit increase in each measure of modifiable CV risk and PWV, respectively.

Table 4.2 displays the results of analyses in which Global Cognition was the outcome. Figures 4.2 and 4.3 illustrate the unadjusted associations between systolic BP and PWV, and PWV and Global Cognition, respectively, by ApoE genotype. Beginning with ApoE ε4 carriers, significant indirect effects were observed for systolic BP, fasting glucose, HDL-C and FRS. Systolic BP, fasting glucose and FRS were positively associated with PWV and PWV was negatively associated with Global Cognition (all $P<0.050$). HDL-C was negatively associated with PWV ($P=0.003$) and PWV was negatively associated with Global Cognition ($P=0.026$). HDL-C was the only measure to have a significant total effect and was positively associated with Global Cognition ($P=0.040$). Figure 4.4 illustrates the full mediation pathway for systolic BP and Global Cognition. No significant indirect effects were observed for any measure of modifiable CV risk in ApoE ε4 noncarriers, indicating that mediation did not occur. Although mediation was observed in ApoE ε4 carriers and not noncarriers, most paths did not significantly differ between groups when compared using Wald χ^2 tests. Path B was an exception for systolic BP and FRS and was significantly stronger in ApoE ε4 carriers

Table 4.3 displays the results of analyses in which GMS was the outcome. No significant indirect effects were observed for any measure of modifiable CV risk in carriers or noncarriers of the ApoE ε4 allele, indicating that no mediation occurred.

Table 4.4 displays the results of analyses in which AR was the outcome. Beginning with ApoE ε4 carriers, significant indirect effects were observed for systolic BP and fasting glucose. Both measures of modifiable CV risk were positively associated with PWV and PWV was negatively associated with AR (all $P<0.050$). Neither measure had a significant total effect on AR. No significant indirect effects were observed for any measure of modifiable CV risk in ApoE ε4 noncarriers, indicating that no mediation occurred. Although mediation was observed in ApoE ε4 carriers and not noncarriers, most paths did not significantly differ between groups when compared using Wald χ^2 tests. Path B was an exception for systolic BP and fasting glucose and was significantly stronger in ApoE ε4 carriers

Table 4.5 displays the results of analyses in which VSOM was the outcome. Beginning with ApoE ε4 carriers, significant indirect effects were observed for systolic BP and FRS. Both measures of modifiable CV risk were positively associated with PWV (both $P<0.001$) and PWV was negatively associated with VSOM (both $P<0.050$). Neither measure had a significant total effect on VSOM. No significant indirect effects were observed for any measure of modifiable CV risk in noncarriers of the ApoE ε4 allele, indicating that no mediation occurred. Although mediation was observed in ApoE ε4 carriers and not noncarriers, most paths did not significantly differ between groups when compared using Wald χ^2 tests. Path B was an exception for systolic BP and FRS and was significantly stronger in ApoE ε4 carriers.

Table 4.6 displays the results of analyses in which Naming was the outcome. Beginning with ApoE ε4 carriers, significant indirect effects were observed for systolic BP and fasting glucose. Both measures of modifiable CV risk were positively associated with PWV and PWV was negatively associated with Naming (all $P<0.050$). Neither measure had a significant to total effect on Naming. No significant indirect effects were observed for any measure of modifiable CV risk in noncarriers of the ApoE ε4 allele, indicating that no mediation occurred. Although mediation was observed in ApoE ε4 carriers and not noncarriers, most paths did not significantly differ between groups when compared using Wald χ^2 tests. Path B was an exception for systolic BP and fasting glucose and was significantly stronger in ApoE ε4 carriers

Table 4.7 displays the results of analyses in which ST was the outcome. Beginning with ApoE ε4 carriers, significant indirect effects were observed for systolic BP and FRS. Both measures of modifiable CV risk were positively associated with PWV (both $P<0.001$) and PWV was negatively associated with ST (both $P<0.050$). Neither measure had a significant total effect on ST. No significant indirect effects were observed for any measure of modifiable CV risk in noncarriers of the ApoE ε4 allele, indicating that no mediation occurred. Although mediation was observed in ApoE ε4 carriers and not noncarriers, no paths significantly differed between groups when compared using Wald χ^2 tests.

Table 4.8 displays the results of analyses in which VC was the outcome. Beginning with ApoE ε4 carriers, significant indirect effects were observed for fasting glucose. Fasting glucose was positively associated with PWV and PWV was negatively associated with VC (both $P<0.050$). Fasting glucose did not have a significant total effect on VC. No significant indirect effects were observed for any measure of modifiable

CV risk in noncarriers of the ApoE ε4 allele, indicating that no mediation occurred. Although mediation was observed in ApoE ε4 carriers and not noncarriers, no paths significantly differed between groups when compared using Wald χ^2 tests.

Table 4.9 displays the results of analyses in which VEM was the outcome. Beginning with ApoE ε4 carriers, significant indirect effects were observed for systolic BP and FRS. Both measures of modifiable CV risk were positively associated with PWV (both $P<0.001$) and PWV was negatively associated with VEM (both $P<0.050$). Neither measure had a significant total effect on VEM. No significant indirect effects were observed for any measure of modifiable CV risk in noncarriers of the ApoE ε4 allele, indicating that no mediation occurred. Although mediation was observed in ApoE ε4 carriers and not noncarriers, most paths did not significantly differ between groups when compared using Wald χ^2 tests. Path B was an exception for systolic BP and fasting glucose and was significantly stronger in ApoE ε4 carriers

Table 4.10 displays the results of analyses in which WM was the outcome. No significant indirect effects were observed for any measure of modifiable CV risk in carriers or noncarriers of the ApoE ε4 allele, indicating that no mediation occurred.

Table 4.2. Pulse wave velocity of a mediator of associations between modifiable cardiovascular risk and Global Cognition.

Measure of Risk	ApoE genotype	Measure	Effect			
			Total	Direct	Indirect	
				Risk → Global	Risk → PWV → Global	
Systolic BP	ApoE ε4 noncarrier	β	-0.0331	-0.0341	0.2957***	0.0024
		b	-0.0016	-0.0016	0.0443	0.0008
		95% LCL	-0.0056,	-0.0062,	0.0308,	-0.0284,
		95% UCL	0.0024	0.0029	0.0578	0.0299
		P-value	0.440	0.474	<0.001	0.958
	ApoE ε4 carrier	β	0.0730	0.1617*	0.3674***	-0.2414**
		b	0.0037	0.0083	0.0575	-0.0789
		95% LCL	-0.0029,	0.0013,	0.0343,	-0.1319,
		95% UCL	0.0104	0.0153	0.0806	-0.0260
		P-value	0.271	0.021	<0.001	0.003
	Comparison	χ^2	1.94	5.51*	0.89	6.42*
		P-value	0.164	0.019	0.346	0.011
Diastolic BP	ApoE ε4 noncarrier	β	-0.0158	-0.0140	0.1879***	-0.0105
		b	-0.0016	-0.0014	0.0585	-0.0034
		95% LCL	-0.0108,	-0.0108,	0.0304,	-0.0296,
		95% UCL	0.0076	0.0079	0.0866	0.0229
		P-value	0.736	0.769	<0.001	0.800
	ApoE ε4 carrier	β	0.1213*	0.1256*	0.0234	-0.1837**
		b	0.0136	0.0140	0.0080	-0.0599
		95% LCL	0.0002,	0.0009,	-0.0469,	-0.1043,
		95% UCL	0.0269	0.0271	0.0630	-0.0155
		P-value	0.047	0.036	0.775	0.008
	Comparison	χ^2	3.4859	3.5615	2.5382	4.5007*
		P-value	0.062	0.059	0.111	0.034

Table 4.2 continued.

Fasting glucose	ApoE ε4 noncarrier	β	-0.0061	-0.0036	0.1925**	-0.0129
		b	-0.0002	-0.0001	0.0247	-0.0041
		95% LCL	-0.0034,	-0.0032,	0.0083,	-0.0324,
		95% UCL	0.0029	0.0029	0.0411	0.0242
		P-value	0.875	0.925	0.003	0.775
	ApoE ε4 carrier	β	-0.0623	-0.0202	0.2409*	-0.1744*
		b	-0.0024	-0.0008	0.0290	-0.0559
		95% LCL	-0.0063,	-0.0047,	0.0035,	-0.1041,
		95% UCL	0.0015	0.0032	0.0544	-0.0076
		P-value	0.233	0.698	0.026	0.023
	Comparison	χ^2	0.73	0.06	0.08	3.20
		P-value	0.394	0.805	0.776	0.074
HDL-C	ApoE ε4 noncarrier	β	0.0642	0.0640	-0.0762	-0.0023
		b	0.0042	0.0041	-0.0154	-0.0008
		95% LCL	-0.0002,	-0.0002,	-0.0348,	-0.0272,
		95% UCL	0.0085	0.0085	0.0040	0.0257
		P-value	0.060	0.062	0.121	0.956
	ApoE ε4 carrier	β	0.1098*	0.0755	-0.2133**	-0.1609*
		b	0.0072	0.0049	-0.0429	-0.0524
		95% LCL	0.0003,	-0.0025,	-0.0714,	-0.0986,
		95% UCL	0.0141	0.0124	-0.0145	-0.0063
		P-value	0.040	0.195	0.003	0.026
	Comparison	χ^2	0.51	0.03	2.45	3.57
		P-value	0.474	0.857	0.117	0.059

Table 4.2 continued.

FRS	ApoE ε4 noncarrier	β	-0.0812**	-0.0943**	0.3415***	0.0383
		b	-0.0214	-0.0248	0.2794	0.0123
		95% LCL	-0.0375,	-0.0431,	0.2092,	-0.0179,
		95% UCL	-0.0053	-0.0065	0.3496	0.0425
		P-value	0.009	0.008	<0.001	0.424
	ApoE ε4 carrier	β	-0.0266	0.0711	0.4501***	-0.2170**
		b	-0.0072	0.0193	0.3754	-0.0707
		95% LCL	-0.0397,	-0.0163,	0.2667,	-0.1230,
		95% UCL	0.0253	0.0550	0.4842	-0.0185
		P-value	0.663	0.288	<0.001	0.008
	Comparison	χ^2	0.58	4.49*	2.14	6.83**
		P-value	0.447	0.034	0.144	0.009
MSLS-CVRFS	ApoE ε4 noncarrier	β	-0.0891*	-0.0991*	0.3067***	0.0325
		b	-0.0560	-0.0622	0.6000	0.0104
		95% LCL	-0.1004,	-0.1116,	0.4298,	-0.0188,
		95% UCL	-0.0116	-0.0129	0.7702	0.0397
		P-value	0.014	0.014	<0.001	0.484
	ApoE ε4 carrier	β	-0.1242*	-0.0593	0.4415***	-0.1468
		b	-0.0778	-0.0372	0.8520	-0.0477
		95% LCL	-0.1465,	-0.1162,	0.5613,	-0.0993,
		95% UCL	-0.0091	0.0419	1.1427	0.0039
		P-value	0.026	0.357	<0.001	0.070
	Comparison	χ^2	0.28	0.28	2.09	3.87*
		P-value	0.594	0.599	0.149	0.049

*P<0.050; **P<0.010; ***P<0.001.

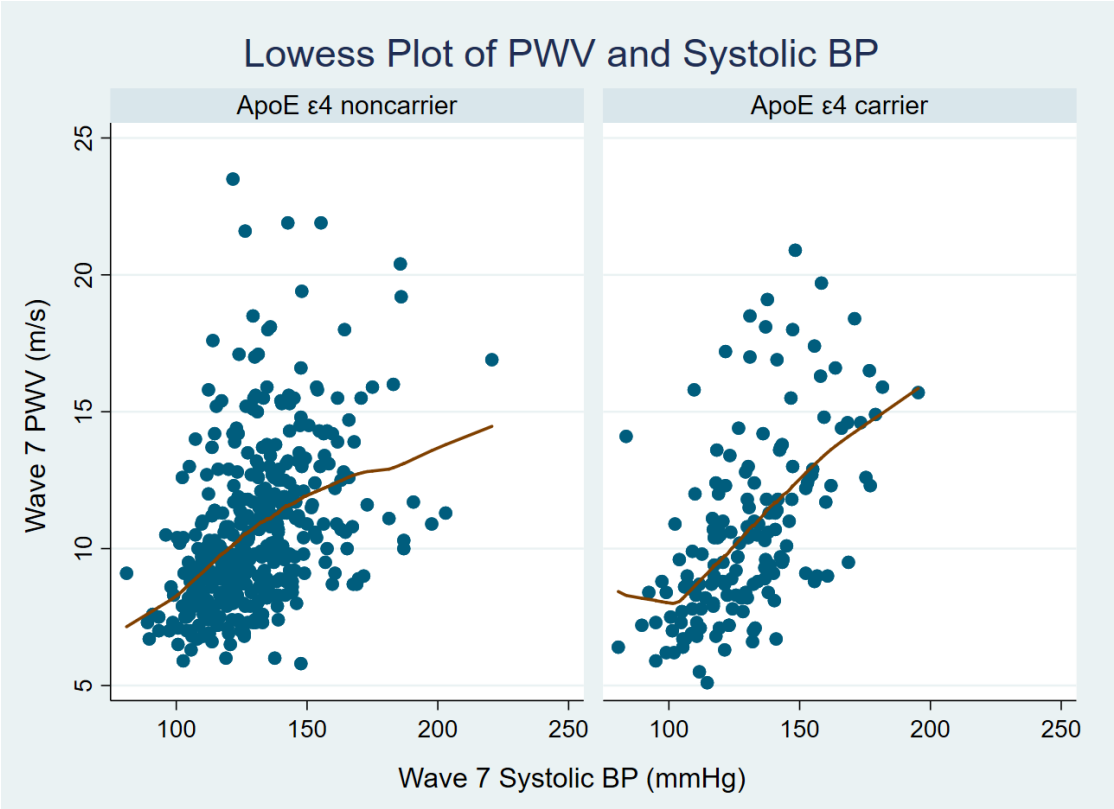

Figure 4.2. Lowess plot of pulse wave velocity and systolic blood pressure, by apolipoprotein E genotype, in cross-sectional analyses.

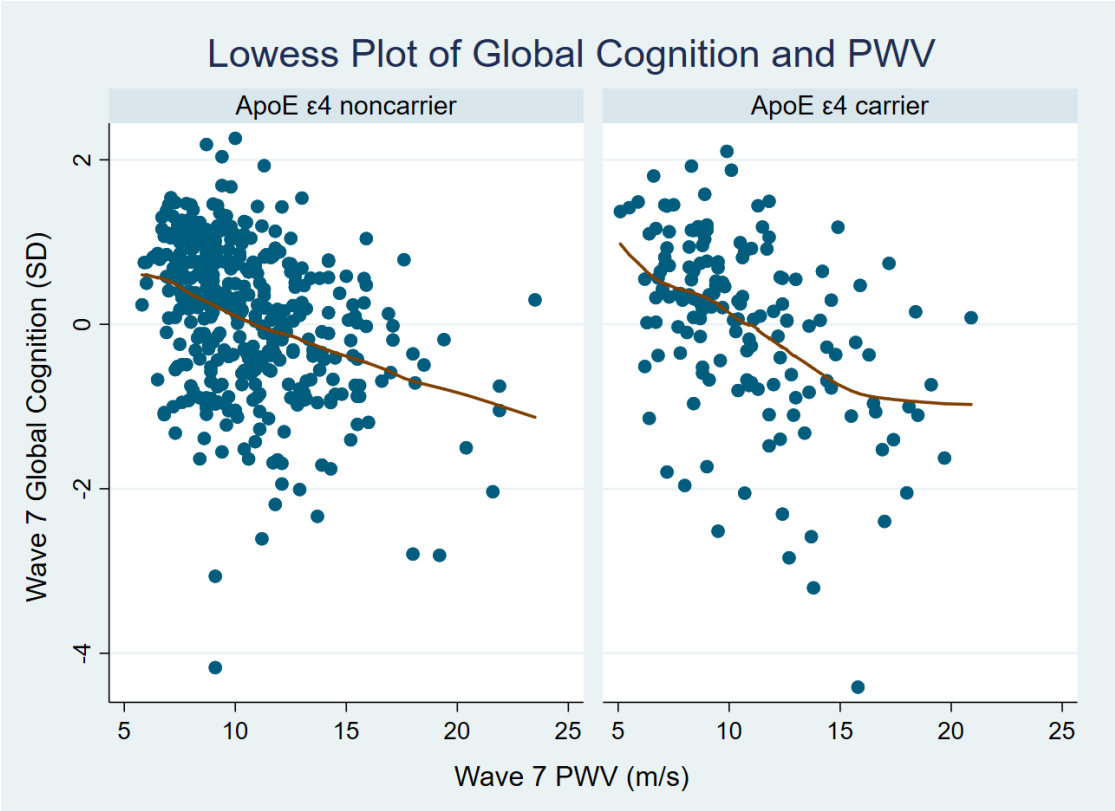

Figure 4.3. Lowess plot of Global Cognition and pulse wave velocity, by apolipoprotein E genotype, in cross-sectional analyses.

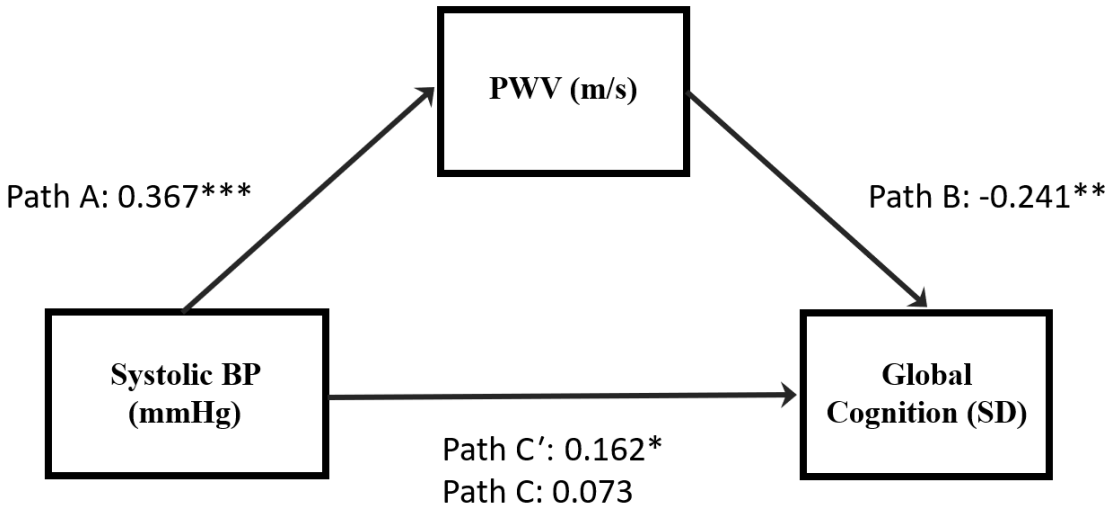

Figure 4.4. Standardized regression coefficients for the association between systolic blood pressure and Global Cognition, as mediated by pulse wave velocity in Apolipoprotein E ε4 carriers. *P<0.050; **P<0.010; ***P<0.001.

Table 4.3. Pulse wave velocity of a mediator of associations between modifiable cardiovascular risk and General Mental State

Measure of Risk	ApoE genotype	Measure	Effect			
			Total	Direct	Indirect	
				Risk → GMS	Risk → PWV → GMS	
Systolic BP	ApoE ε4 noncarrier	β	-0.0206	-0.0394	0.2952***	0.0633
		b	-0.0010	-0.0019	0.0442	0.0201
		95% LCL	-0.0056,	-0.0072,	0.0305,	-0.0165,
		95% UCL	0.0037	0.0035	0.0580	0.0568
		P-value	0.681	0.492	<0.001	0.282
	ApoE ε4 carrier	β	0.0799	0.1088	0.3704***	-0.0781
		b	0.0042	0.0057	0.0581	-0.0259
		95% LCL	-0.0026,	-0.0018,	0.0352,	-0.0772,
		95% UCL	0.0109	0.0131	0.0810	0.0253
		P-value	0.228	0.138	<0.001	0.321
	Comparison	χ^2	1.37	2.56	1.08	2.16
		P-value	0.242	0.110	0.300	0.142
Diastolic BP	ApoE ε4 noncarrier	β	0.0135	0.0039	0.1875***	0.0516
		b	0.0013	0.0004	0.0584	0.0164
		95% LCL	-0.0076,	-0.0088,	0.0313,	-0.0179,
		95% UCL	0.0103	0.0096	0.0854	0.0506
		P-value	0.771	0.934	<0.001	0.349
	ApoE ε4 carrier	β	0.0936	0.0944	0.0237	-0.0363
		b	0.0106	0.0107	0.0082	-0.0120
		95% LCL	-0.0044,	-0.0044,	-0.0457,	-0.0591,
		95% UCL	0.0257	0.0259	0.0620	0.0351
		P-value	0.167	0.164	0.767	0.617
	Comparison	χ^2	1.04	1.28	2.70	0.91
		P-value	0.309	0.257	0.100	0.340

Table 4.3 continued.

Fasting glucose	ApoE ε4 noncarrier	β	-0.0191	-0.0280	0.1900**	0.0470
		b	-0.0008	-0.0011	0.0244	0.0149
		95% LCL	-0.0052,	-0.0056,	0.0091,	-0.0186,
		95% UCL	0.0036	0.0034	0.0396	0.0483
		P-value	0.730	0.622	0.002	0.384
	ApoE ε4 carrier	β	-0.0096	-0.0052	0.2460*	-0.0177
		b	-0.0004	-0.0002	0.0297	-0.0057
		95% LCL	-0.0061,	-0.0066,	0.0030,	-0.0530,
		95% UCL	0.0054	0.0062	0.0564	0.0415
		P-value	0.898	0.950	0.029	0.811
	Comparison	χ^2	0.01	0.06	0.12	0.50
		P-value	0.917	0.814	0.732	0.481
HDL-C	ApoE ε4 noncarrier	β	0.0491	0.0534	-0.0751	0.0566
		b	0.0031	0.0034	-0.0152	0.0179
		95% LCL	-0.0022,	-0.0019,	-0.0331,	-0.0164,
		95% UCL	0.0085	0.0088	0.0028	0.0523
		P-value	0.248	0.212	0.098	0.306
	ApoE ε4 carrier	β	0.0447	0.0401	-0.2136**	-0.0215
		b	0.0030	0.0027	-0.0430	-0.0071
		95% LCL	-0.0046,	-0.0051,	-0.0710,	-0.0545,
		95% UCL	0.0105	0.0104	-0.0151	0.0403
		P-value	0.439	0.500	0.003	0.769
	Comparison	χ^2	0.00	0.02	2.69	0.74
		P-value	0.973	0.878	0.101	0.388

Table 4.3 continued.

FRS	ApoE ε4 noncarrier	β	-0.0579	-0.0854	0.3398***	0.0810
		b	-0.0150	-0.0222	0.2777	0.0257
		95% LCL	-0.0369,	-0.0469,	0.2074,	-0.0108,
		95% UCL	0.0069	0.0026	0.3480	0.0622
		P-value	0.179	0.079	<0.001	0.167
	ApoE ε4 carrier	β	0.0216	0.0499	0.4504***	-0.0629
		b	0.0060	0.0138	0.3763	-0.0208
		95% LCL	-0.0303,	-0.0335,	0.2650,	-0.0777,
		95% UCL	0.0423	0.0612	0.4877	0.0360
		P-value	0.747	0.568	<0.001	0.473
	Comparison	χ^2	0.90	1.75	2.21	1.81
		P-value	0.343	0.186	0.137	0.178
MSLS-CVRFS	ApoE ε4 noncarrier	β	-0.0563	-0.0810	0.3058***	0.0806
		b	-0.0349	-0.0502	0.5980	0.0255
		95% LCL	-0.0836,	-0.1062,	0.4220,	-0.0114,
		95% UCL	0.0138	0.0059	0.7739	0.0624
		P-value	0.160	0.079	<0.001	0.175
	ApoE ε4 carrier	β	-0.0348	-0.0270	0.4430***	-0.0177
		b	-0.0222	-0.0172	0.8564	-0.0058
		95% LCL	-0.1130,	-0.1253,	0.5684,	-0.0622,
		95% UCL	0.0687	0.0909	1.1444	0.0506
		P-value	0.632	0.755	<0.001	0.839
	Comparison	χ^2	0.06	0.27	2.13	0.85
		P-value	0.812	0.601	0.145	0.356

*P<0.050; **P<0.010; ***P<0.001.

Table 4.4. Pulse wave velocity of a mediator of associations between modifiable cardiovascular risk and Abstract Reasoning.

Measure of Risk	ApoE genotype	Measure	Effect			
			Total	Direct	Indirect	
				Risk → AR	Risk → PWV → AR	
Systolic BP	ApoE ε4 noncarrier	β	0.0425	0.0347	0.2956***	0.0262
		b	0.0021	0.0017	0.0443	0.0087
		95% LCL	-0.0029,	-0.0038,	0.0309,	-0.0308,
		95% UCL	0.0071	0.0072	0.0577	0.0481
		P-value	0.407	0.539	<0.001	0.667
	ApoE ε4 carrier	β	0.0183	0.0919	0.3646***	-0.2018*
		b	0.0009	0.0044	0.0571	-0.0623
		95% LCL	-0.0059,	-0.0024,	0.0346,	-0.1120,
		95% UCL	0.0076	0.0113	0.0795	-0.0126
		P-value	0.797	0.204	<0.001	0.014
	Comparison	χ^2	0.08	0.37	0.87	4.70*
		P-value	0.772	0.542	0.350	0.030
Diastolic BP	ApoE ε4 noncarrier	β	0.0020	-0.0049	0.1868***	0.0370
		b	0.0002	-0.0005	0.0581	0.0122
		95% LCL	-0.0108,	-0.0117,	0.0306,	-0.0250,
		95% UCL	0.0112	0.0107	0.0856	0.0493
		P-value	0.971	0.930	<0.001	0.520
	ApoE ε4 carrier	β	0.0247	0.0274	0.0151	-0.1777*
		b	0.0026	0.0029	0.0052	-0.0547
		95% LCL	-0.0108,	-0.0101,	-0.0498,	-0.1010,
		95% UCL	0.0160	0.0159	0.0602	-0.0085
		P-value	0.703	0.663	0.853	0.020
	Comparison	χ^2	0.08	0.15	2.85	5.09*
		P-value	0.784	0.699	0.091	0.024

Table 4.4 continued.

Fasting glucose	ApoE ε4 noncarrier	β	0.0024	-0.0059	0.1917**	0.0396
		b	0.0001	-0.0002	0.0246	0.0130
		95% LCL	-0.0051,	-0.0055,	0.0097,	-0.0234,
		95% UCL	0.0053	0.0050	0.0395	0.0494
		P-value	0.970	0.927	0.001	0.484
	ApoE ε4 carrier	β	-0.0075	0.0347	0.2379*	-0.1773*
		b	-0.0003	0.0013	0.0286	-0.0537
		95% LCL	-0.0040,	-0.0026,	0.0030,	-0.1010,
		95% UCL	0.0034	0.0051	0.0543	-0.0063
		P-value	0.886	0.520	0.029	0.026
	Comparison	χ^2	0.01	0.20	0.07	4.57*
		P-value	0.917	0.654	0.790	0.032
HDL-C	ApoE ε4 noncarrier	β	0.0549	0.0596	-0.0766	0.0480
		b	0.0036	0.0040	-0.0154	0.0158
		95% LCL	-0.0021,	-0.0019,	-0.0335,	-0.0208,
		95% UCL	0.0094	0.0098	0.0026	0.0524
		P-value	0.211	0.184	0.094	0.397
	ApoE ε4 carrier	β	0.1197	0.0881	-0.2105**	-0.1504
		b	0.0074	0.0055	-0.0424	-0.0463
		95% LCL	-0.0000,	-0.0012,	-0.0699,	-0.0927,
		95% UCL	0.0149	0.0121	-0.0148	0.0001
		P-value	0.050	0.108	0.003	0.051
	Comparison	χ^2	0.65	0.11	2.58	4.51*
		P-value	0.419	0.735	0.109	0.034

Table 4.4 continued.

FRS	ApoE ε4 noncarrier	β	0.0070	-0.0085	0.3410***	0.0456
		b	0.0019	-0.0023	0.2790	0.0150
		95% LCL	-0.0216,	-0.0278,	0.2071,	-0.0239,
		95% UCL	0.0254	0.0232	0.3509	0.0540
		P-value	0.874	0.859	<0.001	0.448
	ApoE ε4 carrier	β	-0.0826	-0.0181	0.4459***	-0.1448
		b	-0.0212	-0.0047	0.3718	-0.0446
		95% LCL	-0.0552,	-0.0412,	0.2641,	-0.0927,
		95% UCL	0.0127	0.0319	0.4795	0.0035
		P-value	0.220	0.803	<0.001	0.069
	Comparison	χ^2	1.13	0.01	2.05	3.63
		P-value	0.288	0.919	0.152	0.057
MSLS-CVRFS	ApoE ε4 noncarrier	β	-0.0793	-0.1077*	0.3079***	0.0925
		b	-0.0511	-0.0694	0.6027	0.0304
		95% LCL	-0.1087,	-0.1347,	0.4306,	-0.0096,
		95% UCL	0.0066	-0.0042	0.7748	0.0705
		P-value	0.082	0.037	<0.001	0.137
	ApoE ε4 carrier	β	-0.1164	-0.0583	0.4400***	-0.1321
		b	-0.0689	-0.0345	0.8489	-0.0406
		95% LCL	-0.1536,	-0.1272,	0.5732,	-0.0922,
		95% UCL	0.0157	0.0582	1.1247	0.0111
		P-value	0.110	0.466	<0.001	0.124
	Comparison	χ^2	0.11	0.35	2.19	4.56*
		P-value	0.742	0.555	0.139	0.033

*P<0.050; **P<0.010; ***P<0.001.

Table 4.5. Pulse wave velocity of a mediator of associations between modifiable cardiovascular risk and Visual-Spatial Organization/Memory.

Measure of Risk	ApoE genotype	Measure	Effect			
			Total	Direct	Indirect	
				Risk → VSOM	Risk → PWV → VSOM	
Systolic BP	ApoE ε4 noncarrier	β	-0.066	-0.071	0.296***	0.015
		b	-0.003	-0.004	0.044	0.005
		95% LCL	-0.0075,	-0.0081,	0.0309,	-0.0258,
		95% UCL	0.0010	0.0010	0.0577	0.0357
		P-value	0.130	0.129	<0.001	0.753
	ApoE ε4 carrier	β	0.122	0.208**	0.363***	-0.238**
		b	0.006	0.010	0.057	-0.073
		95% LCL	-0.0005,	0.0030,	0.0347,	-0.1255,
		95% UCL	0.0122	0.0171	0.0793	-0.0202
		P-value	0.069	0.005	<0.001	0.007
	Comparison	χ^2	5.41*	9.57**	0.95	6.46*
		P-value	0.020	0.002	0.331	0.011
Diastolic BP	ApoE ε4 noncarrier	β	-0.024	-0.023	0.188***	-0.009
		b	-0.002	-0.002	0.058	-0.003
		95% LCL	-0.0117,	-0.0126,	0.0298,	-0.0327,
		95% UCL	0.0067	0.0079	0.0871	0.0265
		P-value	0.596	0.656	<0.001	0.836
	ApoE ε4 carrier	β	0.153*	0.157*	0.020	-0.166*
		b	0.016	0.017	0.007	-0.051
		95% LCL	0.0034,	0.0036,	-0.0463,	-0.0985,
		95% UCL	0.0289	0.0294	0.0602	-0.0029
		P-value	0.013	0.012	0.797	0.038
	Comparison	χ^2	4.96*	4.97*	2.72	2.73
		P-value	0.026	0.026	0.099	0.098

Table 4.5 continued.

Fasting glucose	ApoE ε4 noncarrier	β	-0.027	-0.025	0.192**	-0.009
		b	-0.001	-0.001	0.025	-0.003
		95% LCL	-0.0039,	-0.0040,	0.0093,	-0.0337,
		95% UCL	0.0016	0.0019	0.0401	0.0280
		P-value	0.412	0.475	0.002	0.856
	ApoE ε4 carrier	β	-0.060	-0.020	0.247*	-0.162
		b	-0.002	-0.001	0.030	-0.048
		95% LCL	-0.0060,	-0.0047,	0.0043,	-0.0970,
		95% UCL	0.0017	0.0032	0.0554	0.0001
		P-value	0.271	0.723	0.022	0.050
	Comparison	χ^2	0.17	0.02	0.12	2.50
		P-value	0.677	0.889	0.733	0.114
HDL-C	ApoE ε4 noncarrier	β	0.061	0.061	-0.076	-0.004
		b	0.004	0.004	-0.015	-0.001
		95% LCL	-0.0007,	-0.0009,	-0.0338,	-0.0328,
		95% UCL	0.0089	0.0090	0.0031	0.0299
		P-value	0.097	0.109	0.103	0.929
	ApoE ε4 carrier	β	0.099	0.069	-0.212**	-0.144
		b	0.006	0.004	-0.043	-0.044
		95% LCL	-0.0012,	-0.0033,	-0.0700,	-0.0936,
		95% UCL	0.0134	0.0118	-0.0158	0.0055
		P-value	0.099	0.270	0.002	0.082
	Comparison	χ^2	0.24	0.00	2.63	2.10
		P-value	0.625	0.965	0.105	0.147

Table 4.5 continued.

FRS	ApoE ε4 noncarrier	β	-0.088**	-0.102**	0.341***	0.040
		b	-0.024	-0.028	0.279	0.013
		95% LCL	-0.0416,	-0.0479,	0.2095,	-0.0196,
		95% UCL	-0.0061	-0.0072	0.3493	0.0458
		P-value	0.008	0.008	<0.001	0.432
	ApoE ε4 carrier	β	0.005	0.094	0.445***	-0.201*
		b	0.001	0.024	0.372	-0.061
		95% LCL	-0.0290,	-0.0103,	0.2615,	-0.1149,
		95% UCL	0.0313	0.0585	0.4834	-0.0081
		P-value	0.938	0.170	<0.001	0.024
	Comparison	χ^2	1.91	6.10*	1.96	5.49*
		P-value	0.168	0.013	0.161	0.019
MSLS-CVRFS	ApoE ε4 noncarrier	β	-0.076*	-0.082*	0.306***	0.019
		b	-0.049	-0.053	0.599	0.006
		95% LCL	-0.0950,	-0.1001,	0.4239,	-0.0273,
		95% UCL	-0.0037	-0.0062	0.7751	0.0400
		P-value	0.034	0.027	<0.001	0.712
	ApoE ε4 carrier	β	-0.100	-0.041	0.440***	-0.133
		b	-0.059	-0.024	0.851	-0.040
		95% LCL	-0.1300,	-0.1072,	0.5714,	-0.0939,
		95% UCL	0.0127	0.0587	1.1312	0.0130
		P-value	0.107	0.567	<0.001	0.138
	Comparison	χ^2	0.05	0.34	2.24	2.02
		P-value	0.823	0.557	0.135	0.155

*P<0.050; **P<0.010; ***P<0.001.

Table 4.6. Pulse wave velocity of a mediator of associations between modifiable cardiovascular risk and Naming.

Measure of Risk	ApoE genotype	Measure	Effect			
			Total	Direct	Indirect	
				Risk → Naming	Risk → PWV → Naming	
Systolic BP	ApoE ε4 noncarrier	β	0.0616	0.0478	0.2957***	0.0465
		b	0.0030	0.0023	0.0443	0.0153
		95% LCL	-0.0036,	-0.0047,	0.0307,	-0.0248,
		95% UCL	0.0097	0.0094	0.0579	0.0553
		P-value	0.371	0.516	<0.001	0.455
	ApoE ε4 carrier	β	0.0582	0.1344	0.3714***	-0.2052*
		b	0.0029	0.0066	0.0582	-0.0646
		95% LCL	-0.0073,	-0.0057,	0.0352,	-0.1270,
		95% UCL	0.0130	0.0189	0.0812	-0.0021
		P-value	0.580	0.291	<0.001	0.043
	Comparison	χ^2	0.00	0.35	1.01	4.50*
		P-value	0.981	0.555	0.316	0.034
Diastolic BP	ApoE ε4 noncarrier	β	0.0513	0.0414	0.1868***	0.0527
		b	0.0052	0.0042	0.0581	0.0172
		95% LCL	-0.0087,	-0.0100,	0.0306,	-0.0168,
		95% UCL	0.0191	0.0184	0.0857	0.0512
		P-value	0.461	0.560	<0.001	0.321
	ApoE ε4 carrier	β	0.0492	0.0527	0.0233	-0.1492*
		b	0.0053	0.0057	0.0080	-0.0469
		95% LCL	-0.0091,	-0.0079,	-0.0472,	-0.0901,
		95% UCL	0.0197	0.0193	0.0632	-0.0036
		P-value	0.470	0.413	0.776	0.034
	Comparison	χ^2	0.00	0.02	2.57	5.20*
		P-value	0.993	0.883	0.109	0.023

Table 4.6 continued.

Fasting glucose	ApoE ε4 noncarrier	β	-0.0340	-0.0470	0.1901**	0.0674
		b	-0.0014	-0.0020	0.0244	0.0220
		95% LCL	-0.0053,	-0.0061,	0.0089,	-0.0136,
		95% UCL	0.0025	0.0022	0.0398	0.0575
		P-value	0.475	0.354	0.002	0.226
	ApoE ε4 carrier	β	0.0044	0.0397	0.2400*	-0.1471*
		b	0.0002	0.0015	0.0289	-0.0454
		95% LCL	-0.0052,	-0.0043,	0.0033,	-0.0891,
		95% UCL	0.0055	0.0072	0.0544	-0.0018
		P-value	0.953	0.616	0.027	0.041
	Comparison	χ^2	0.19	0.90	0.09	5.46*
		P-value	0.660	0.342	0.764	0.019
HDL-C	ApoE ε4 noncarrier	β	0.0987*	0.1048*	-0.0773	0.0783
		b	0.0065	0.0069	-0.0156	0.0256
		95% LCL	0.0005,	0.0004,	-0.0347,	-0.0110,
		95% UCL	0.0126	0.0134	0.0035	0.0622
		P-value	0.034	0.036	0.110	0.171
	ApoE ε4 carrier	β	0.1104	0.0833	-0.2133**	-0.1270
		b	0.0070	0.0053	-0.0430	-0.0399
		95% LCL	-0.0004,	-0.0022,	-0.0697,	-0.0815,
		95% UCL	0.0144	0.0128	-0.0162	0.0017
		P-value	0.065	0.170	0.002	0.060
	Comparison	χ^2	0.01	0.10	2.62	5.25*
		P-value	0.927	0.748	0.106	0.022

Table 4.6 continued.

FRS	ApoE ε4 noncarrier	β	-0.0444	-0.0773	0.3407***	0.0965
		b	-0.0119	-0.0207	0.2785	0.0316
		95% LCL	-0.0302,	-0.0434,	0.2090,	-0.0098,
		95% UCL	0.0064	0.0021	0.3480	0.0730
		P-value	0.203	0.075	<0.001	0.134
	ApoE ε4 carrier	β	-0.0445	0.0299	0.4503***	-0.1653
		b	-0.0117	0.0078	0.3761	-0.0519
		95% LCL	-0.0514,	-0.0394,	0.2659,	-0.1057,
		95% UCL	0.0280	0.0551	0.4862	0.0019
		P-value	0.564	0.745	<0.001	0.059
	Comparison	χ^2	0.00	1.16	2.15	5.91*
		P-value	0.993	0.282	0.142	0.015
MSLS-CVRFS	ApoE ε4 noncarrier	β	-0.0850	-0.1197	0.3067***	0.1131
		b	-0.0543	-0.0765	0.5996	0.0370
		95% LCL	-0.1204,	-0.1619,	0.4260,	-0.0073,
		95% UCL	0.0118	0.0089	0.7731	0.0813
		P-value	0.107	0.079	<0.001	0.102
	ApoE ε4 carrier	β	-0.0934	-0.0385	0.4419***	-0.1242
		b	-0.0564	-0.0233	0.8534	-0.0389
		95% LCL	-0.1311,	-0.0984,	0.5689,	-0.0829,
		95% UCL	0.0183	0.0519	1.1379	0.0052
		P-value	0.139	0.544	<0.001	0.084
	Comparison	χ^2	0.00	0.87	2.33	5.62*
		P-value	0.967	0.352	0.127	0.018

*P<0.050; **P<0.010; ***P<0.001.

Table 4.7. Pulse wave velocity of a mediator of associations between modifiable cardiovascular risk and Scanning and Tracking.

Measure of Risk	ApoE genotype	Measure	Effect			
			Total	Direct	Indirect	
				Risk → ST	Risk → PWV → ST	
Systolic BP	ApoE ε4 noncarrier	β	-0.0160	-0.0093	0.2956***	-0.0237
		b	-0.0008	-0.0004	0.0443	-0.0076
		95% LCL	-0.0047,	-0.0047,	0.0308,	-0.0360,
		95% UCL	0.0032	0.0038	0.0579	0.0208
		P-value	0.701	0.838	<0.001	0.600
	ApoE ε4 carrier	β	0.0696	0.1392*	0.3667***	-0.1900*
		b	0.0036	0.0071	0.0575	-0.0622
		95% LCL	-0.0028,	0.0006,	0.0362,	-0.1101,
		95% UCL	0.0100	0.0137	0.0788	-0.0144
		P-value	0.273	0.032	<0.001	0.011
	Comparison	χ^2	1.35	3.58	1.07	3.59
		P-value	0.246	0.059	0.302	0.058
Diastolic BP	ApoE ε4 noncarrier	β	0.0071	0.0139	0.1883***	-0.0352
		b	0.0007	0.0014	0.0586	-0.0113
		95% LCL	-0.0077,	-0.0074,	0.0304,	-0.0395,
		95% UCL	0.0091	0.0102	0.0869	0.0169
		P-value	0.868	0.758	<0.001	0.433
	ApoE ε4 carrier	β	0.1290*	0.1326*	0.0247	-0.1431*
		b	0.0145	0.0149	0.0085	-0.0467
		95% LCL	0.0019,	0.0014,	-0.0451,	-0.0893,
		95% UCL	0.0271	0.0284	0.0621	-0.0042
		P-value	0.024	0.031	0.756	0.031
	Comparison	χ^2	3.07	2.88	2.71	1.93
		P-value	0.080	0.090	0.100	0.165

Table 4.7 continued.

Fasting glucose	ApoE ε4 noncarrier	β	0.0321	0.0404	0.1932**	-0.0429
		b	0.0013	0.0017	0.0248	-0.0137
		95% LCL	-0.0017,	-0.0015,	0.0090,	-0.0425,
		95% UCL	0.0044	0.0048	0.0406	0.0152
		P-value	0.399	0.300	0.002	0.353
	ApoE ε4 carrier	β	-0.1004	-0.0718	0.2401*	-0.1191
		b	-0.0039	-0.0028	0.0289	-0.0382
		95% LCL	-0.0078,	-0.0065,	0.0024,	-0.0838,
		95% UCL	0.0001	0.0010	0.0554	0.0073
		P-value	0.055	0.145	0.032	0.100
	Comparison	χ^2	4.66*	3.21	0.07	0.76
		P-value	0.031	0.073	0.792	0.383
HDL-C	ApoE ε4 noncarrier	β	0.0110	0.0088	-0.0761	-0.0280
		b	0.0007	0.0006	-0.0154	-0.0090
		95% LCL	-0.0041,	-0.0041,	-0.0334,	-0.0381,
		95% UCL	0.0055	0.0052	0.0026	0.0202
		P-value	0.773	0.812	0.094	0.547
	ApoE ε4 carrier	β	0.0396	0.0104	-0.2141**	-0.1363
		b	0.0026	0.0007	-0.0432	-0.0445
		95% LCL	-0.0053,	-0.0076,	-0.0706,	-0.0912,
		95% UCL	0.0105	0.0090	-0.0157	0.0022
		P-value	0.517	0.871	0.002	0.062
	Comparison	χ^2	0.17	0.00	2.74	1.59
		P-value	0.684	0.980	0.098	0.207

Table 4.7 continued.

FRS	ApoE ε4 noncarrier	β	-0.0299	-0.0267	0.3407***	-0.0095
		b	-0.0079	-0.0070	0.2788	-0.0030
		95% LCL	-0.0261,	-0.0262,	0.2071,	-0.0329,
		95% UCL	0.0104	0.0122	0.3506	0.0268
		P-value	0.398	0.475	<0.001	0.842
	ApoE ε4 carrier	β	0.0031	0.0841	0.4489***	-0.1803*
		b	0.0009	0.0230	0.3750	-0.0589
		95% LCL	-0.0308,	-0.0161,	0.2650,	-0.1103,
		95% UCL	0.0325	0.0620	0.4850	-0.0076
		P-value	0.958	0.250	<0.001	0.024
	Comparison	χ^2	0.20	1.82	2.10	3.45
		P-value	0.657	0.177	0.147	0.063
MSLS-CVRFS	ApoE ε4 noncarrier	β	-0.0263	-0.0191	0.3065***	-0.0235
		b	-0.0165	-0.0119	0.6001	-0.0075
		95% LCL	-0.0619,	-0.0626,	0.4216,	-0.0394,
		95% UCL	0.0290	0.0388	0.7786	0.0244
		P-value	0.478	0.644	<0.001	0.643
	ApoE ε4 carrier	β	-0.0679	-0.0075	0.4433***	-0.1363
		b	-0.0427	-0.0047	0.8573	-0.0443
		95% LCL	-0.1141,	-0.0904,	0.5646,	-0.0956,
		95% UCL	0.0286	0.0810	1.1500	0.0069
		P-value	0.240	0.914	<0.001	0.090
	Comparison	χ^2	0.37	0.02	2.04	1.43
		P-value	0.542	0.885	0.154	0.232

*P<0.050; **P<0.010; ***P<0.001.

Table 4.8. Pulse wave velocity of a mediator of associations between modifiable cardiovascular risk and Verbal Comprehension.

Measure of Risk	ApoE genotype	Measure	Effect			
			Total	**Direct**	**Indirect**	
				Risk → VC	**Risk → PWV → VC**	
Systolic BP	ApoE ε4 noncarrier	*β*	-0.0378	-0.0362	0.2958***	-0.0052
		b	-0.0018	-0.0017	0.0443	-0.0017
		95% LCL	-0.0059,	-0.0065,	0.0309,	-0.0422,
		95% UCL	0.0022	0.0030	0.0578	0.0388
		P-value	0.376	0.470	<0.001	0.935
	ApoE ε4 carrier	*β*	-0.0877	-0.0444	0.3702***	-0.1168
		b	-0.0045	-0.0023	0.0580	-0.0381
		95% LCL	-0.0106,	-0.0094,	0.0349,	-0.0841,
		95% UCL	0.0017	0.0049	0.0812	0.0078
		P-value	0.153	0.532	<0.001	0.104
	Comparison	χ^2	0.51	0.02	1.02	1.34
		P-value	0.476	0.901	0.312	0.248
Diastolic BP	ApoE ε4 noncarrier	*β*	-0.0672	-0.0664	0.1877***	-0.0038
		b	-0.0067	-0.0066	0.0584	-0.0012
		95% LCL	-0.0163,	-0.0156,	0.0307,	-0.0364,
		95% UCL	0.0029	0.0023	0.0862	0.0340
		P-value	0.169	0.147	<0.001	0.947
	ApoE ε4 carrier	*β*	0.0044	0.0071	0.0197	-0.1369
		b	0.0005	0.0008	0.0068	-0.0446
		95% LCL	-0.0125,	-0.0121,	-0.0480,	-0.0895,
		95% UCL	0.0135	0.0137	0.0616	0.0002
		P-value	0.941	0.904	0.809	0.051
	Comparison	χ^2	0.80	0.86	2.75	2.27
		P-value	0.372	0.354	0.097	0.132

Table 4.8 continued.

Fasting glucose	ApoE ε4 noncarrier	β	-0.0086	-0.0052	0.1928**	-0.0191
		b	-0.0004	-0.0002	0.0247	-0.0061
		95% LCL	-0.0044,	-0.0044,	0.0088,	-0.0427,
		95% UCL	0.0037	0.0040	0.0407	0.0304
		P-value	0.864	0.920	0.002	0.743
	ApoE ε4 carrier	β	-0.0161	0.0201	0.2492*	-0.1452*
		b	-0.0006	0.0008	0.0300	-0.0464
		95% LCL	-0.0051,	-0.0037,	0.0048,	-0.0897,
		95% UCL	0.0038	0.0053	0.0553	-0.0031
		P-value	0.784	0.737	0.020	0.036
	Comparison	χ^2	0.01	0.10	0.12	1.96
		P-value	0.935	0.753	0.725	0.162
HDL-C	ApoE ε4 noncarrier	β	0.0599	0.0597	-0.0763	-0.0058
		b	0.0039	0.0039	-0.0154	-0.0019
		95% LCL	-0.0016,	-0.0017,	-0.0337,	-0.0369,
		95% UCL	0.0094	0.0094	0.0029	0.0332
		P-value	0.165	0.175	0.099	0.918
	ApoE ε4 carrier	β	0.1403*	0.1174*	-0.2141**	-0.1072
		b	0.0092	0.0077	-0.0431	-0.0349
		95% LCL	0.0018,	0.0006,	-0.0710,	-0.0771,
		95% UCL	0.0166	0.0148	-0.0152	0.0072
		P-value	0.015	0.034	0.002	0.104
	Comparison	χ^2	1.32	0.71	2.64	1.55
		P-value	0.251	0.400	0.104	0.213

Table 4.8 continued.

FRS	ApoE ε4 noncarrier	β	-0.0846*	-0.0921*	0.3407***	0.0219
		b	-0.0222	-0.0242	0.2788	0.0070
		95% LCL	-0.0435,	-0.0481,	0.2096,	-0.0329,
		95% UCL	-0.0010	-0.0003	0.3479	0.0469
		P-value	0.040	0.047	<0.001	0.730
	ApoE ε4 carrier	β	-0.1111	-0.0620	0.4513***	-0.1087
		b	-0.0302	-0.0169	0.3770	-0.0354
		95% LCL	-0.0607,	-0.0542,	0.2668,	-0.0865,
		95% UCL	0.0003	0.0205	0.4873	0.0157
		P-value	0.052	0.377	<0.001	0.174
	Comparison	χ^2	0.17	0.10	2.18	1.65
		P-value	0.683	0.749	0.139	0.199
MSLS-CVRFS	ApoE ε4 noncarrier	β	-0.0777	-0.0843	0.3065***	0.0213
		b	-0.0488	-0.0529	0.5998	0.0068
		95% LCL	-0.1006,	-0.1092,	0.4301,	-0.0306,
		95% UCL	0.0031	0.0034	0.7695	0.0443
		P-value	0.065	0.066	<0.001	0.720
	ApoE ε4 carrier	β	-0.1122	-0.0655	0.4436***	-0.1052
		b	-0.0703	-0.0411	0.8568	-0.0342
		95% LCL	-0.1489,	-0.1315,	0.5565,	-0.0859,
		95% UCL	0.0082	0.0494	1.1570	0.0176
		P-value	0.079	0.373	<0.001	0.196
	Comparison	χ^2	0.21	0.05	2.09	1.60
		P-value	0.650	0.827	0.148	0.205

*P<0.050; **P<0.010; ***P<0.001.

Table 4.9. Pulse wave velocity of a mediator of associations between modifiable cardiovascular risk and Verbal Episodic Memory.

Measure of Risk	ApoE genotype	Measure	Effect			
			Total	Direct	Indirect	
				Risk → VEM	Risk → PWV → VEM	
Systolic BP	ApoE ε4 noncarrier	β	0.0458	0.0417	0.2956***	0.0142
		b	0.0022	0.0020	0.0443	0.0046
		95% LCL	-0.0019,	-0.0026,	0.0310,	-0.0284,
		95% UCL	0.0064	0.0067	0.0576	0.0376
		P-value	0.289	0.389	<0.001	0.783
	ApoE ε4 carrier	β	0.0735	0.1551	0.3751***	-0.2176*
		b	0.0037	0.0077	0.0587	-0.0691
		95% LCL	-0.0036,	-0.0003,	0.0356,	-0.1290,
		95% UCL	0.0109	0.0157	0.0818	-0.0091
		P-value	0.323	0.058	<0.001	0.024
	Comparison	χ^2	0.11	1.48	1.11	4.57*
		P-value	0.740	0.224	0.292	0.033
Diastolic BP	ApoE ε4 noncarrier	β	0.0296	0.0249	0.1873***	0.0253
		b	0.0030	0.0025	0.0583	0.0083
		95% LCL	-0.0059,	-0.0070,	0.0311,	-0.0223,
		95% UCL	0.0119	0.0121	0.0855	0.0388
		P-value	0.510	0.604	<0.001	0.597
	ApoE ε4 carrier	β	0.1045	0.1084	0.0268	-0.1482
		b	0.0113	0.0118	0.0092	-0.0470
		95% LCL	-0.0039,	-0.0042,	-0.0457,	-0.1057,
		95% UCL	0.0266	0.0277	0.0641	0.0118
		P-value	0.145	0.148	0.743	0.117
	Comparison	χ^2	0.82	0.97	2.41	2.77
		P-value	0.366	0.324	0.121	0.096

Table 4.9 continued.

Fasting glucose	ApoE ε4 noncarrier	β	0.0738	0.0699	0.1923**	0.0195
		b	0.0031	0.0029	0.0247	0.0063
		95% LCL	-0.0000,	-0.0006,	0.0091,	-0.0240,
		95% UCL	0.0062	0.0064	0.0402	0.0367
		P-value	0.053	0.100	0.002	0.683
	ApoE ε4 carrier	β	0.0081	0.0440	0.2435*	-0.1477
		b	0.0003	0.0016	0.0293	-0.0460
		95% LCL	-0.0045,	-0.0037,	0.0034,	-0.1009,
		95% UCL	0.0051	0.0070	0.0551	0.0090
		P-value	0.902	0.543	0.026	0.101
	Comparison	χ^2	0.82	0.16	0.09	2.67
		P-value	0.365	0.692	0.765	0.102
HDL-C	ApoE ε4 noncarrier	β	0.0177	0.0204	-0.0761	0.0360
		b	0.0012	0.0013	-0.0153	0.0117
		95% LCL	-0.0045,	-0.0044,	-0.0342,	-0.0189,
		95% UCL	0.0069	0.0071	0.0035	0.0423
		P-value	0.689	0.648	0.111	0.453
	ApoE ε4 carrier	β	0.0941	0.0680	-0.2125**	-0.1229
		b	0.0060	0.0043	-0.0427	-0.0389
		95% LCL	-0.0013,	-0.0032,	-0.0701,	-0.0924,
		95% UCL	0.0133	0.0119	-0.0153	0.0145
		P-value	0.108	0.261	0.002	0.153
	Comparison	χ^2	0.96	0.37	2.64	2.66
		P-value	0.327	0.544	0.104	0.103

Table 4.9 continued.

FRS	ApoE ε4 noncarrier	β	-0.0043	-0.0190	0.3412***	0.0432
		b	-0.0011	-0.0051	0.2791	0.0141
		95% LCL	-0.0220,	-0.0300,	0.2066,	-0.0219,
		95% UCL	0.0197	0.0198	0.3515	0.0500
		P-value	0.914	0.689	<0.001	0.443
	ApoE ε4 carrier	β	0.0006	0.0948	0.4547***	-0.2073*
		b	0.0002	0.0250	0.3793	-0.0656
		95% LCL	-0.0385,	-0.0174,	0.2653,	-0.1276,
		95% UCL	0.0388	0.0675	0.4933	-0.0037
		P-value	0.994	0.247	<0.001	0.038
	Comparison	χ^2	0.00	1.42	2.07	4.63*
		P-value	0.953	0.234	0.150	0.031
MSLS-CVRFS	ApoE ε4 noncarrier	β	-0.0437	-0.0619	0.3068***	0.0595
		b	-0.0278	-0.0394	0.6001	0.0194
		95% LCL	-0.0802,	-0.0952,	0.4260,	-0.0148,
		95% UCL	0.0245	0.0164	0.7741	0.0535
		P-value	0.298	0.166	<0.001	0.266
	ApoE ε4 carrier	β	-0.1229	-0.0829	0.4419***	-0.0905
		b	-0.0748	-0.0505	0.8526	-0.0285
		95% LCL	-0.1600,	-0.1495,	0.5613,	-0.0893,
		95% UCL	0.0105	0.0486	1.1438	0.0323
		P-value	0.086	0.318	<0.001	0.358
	Comparison	χ^2	0.84	0.04	2.12	1.80
		P-value	0.361	0.850	0.145	0.180

*P<0.050; **P<0.010; ***P<0.001.

Table 4.10. Pulse wave velocity of a mediator of associations between modifiable cardiovascular risk and Working Memory.

Measure of Risk	ApoE genotype	Measure	Effect			
			Total	Direct	Indirect	
				Risk → WM	Risk → PWV → WM	
Systolic BP	ApoE ε4 noncarrier	β	-0.0882	-0.0825	0.2957***	-0.0215
		b	-0.0042	-0.0039	0.0443	-0.0068
		95% LCL	-0.0085,	-0.0088,	0.0303,	-0.0405,
		95% UCL	0.0002	0.0009	0.0584	0.0269
		P-value	0.064	0.113	<0.001	0.693
	ApoE ε4 carrier	β	0.0178	0.0903	0.3704***	-0.1956
		b	0.0009	0.0048	0.0579	-0.0660
		95% LCL	-0.0074,	-0.0043,	0.0347,	-0.1326,
		95% UCL	0.0092	0.0139	0.0811	0.0005
		P-value	0.824	0.305	<0.001	0.052
	Comparison	χ^2	1.13	2.77	0.91	2.44
		P-value	0.288	0.096	0.340	0.118
Diastolic BP	ApoE ε4 noncarrier	β	-0.0664	-0.0589	0.1879***	-0.0425
		b	-0.0065	-0.0058	0.0585	-0.0134
		95% LCL	-0.0160,	-0.0154,	0.0308,	-0.0454,
		95% UCL	0.0031	0.0038	0.0862	0.0187
		P-value	0.185	0.237	<0.001	0.413
	ApoE ε4 carrier	β	0.0567	0.0608	0.0253	-0.1635
		b	0.0065	0.0070	0.0087	-0.0551
		95% LCL	-0.0111,	-0.0104,	-0.0468,	-0.1135,
		95% UCL	0.0242	0.0245	0.0641	0.0033
		P-value	0.468	0.431	0.759	0.064
	Comparison	χ^2	1.68	1.56	2.45	1.49
		P-value	0.195	0.211	0.118	0.223

Table 4.10 continued.

Fasting glucose	ApoE ε4 noncarrier	β	-0.0734	-0.0658	0.1927**	-0.0414
		b	-0.0029	-0.0027	0.0247	-0.0130
		95% LCL	-0.0067,	-0.0067,	0.0095,	-0.0454,
		95% UCL	0.0008	0.0014	0.0400	0.0194
		P-value	0.119	0.202	0.001	0.432
	ApoE ε4 carrier	β	-0.0744	-0.0371	0.2453*	-0.1521
		b	-0.0030	-0.0015	0.0295	-0.0503
		95% LCL	-0.0081,	-0.0066,	0.0030,	-0.1108,
		95% UCL	0.0022	0.0037	0.0560	0.0102
		P-value	0.258	0.576	0.029	0.103
	Comparison	χ^2	0.00	0.12	0.09	1.17
		P-value	0.997	0.727	0.760	0.280
HDL-C	ApoE ε4 noncarrier	β	0.0936*	0.0907*	-0.0761	-0.0453
		b	0.0059	0.0058	-0.0154	-0.0143
		95% LCL	0.0005,	0.0003,	-0.0342,	-0.0479,
		95% UCL	0.0114	0.0112	0.0035	0.0193
		P-value	0.032	0.037	0.111	0.405
	ApoE ε4 carrier	β	0.1034	0.0724	-0.2154**	-0.1438
		b	0.0070	0.0049	-0.0433	-0.0484
		95% LCL	-0.0028,	-0.0042,	-0.0707,	-0.1068,
		95% UCL	0.0168	0.0140	-0.0159	0.0099
		P-value	0.163	0.293	0.002	0.104
	Comparison	χ^2	0.03	0.03	2.72	0.95
		P-value	0.852	0.871	0.099	0.330

Table 4.10 continued.

FRS	ApoE ε4 noncarrier	β	-0.1469**	-0.1544**	0.3412***	0.0222
		b	-0.0379	-0.0398	0.2792	0.0070
		95% LCL	-0.0598,	-0.0639,	0.2040,	-0.0257,
		95% UCL	-0.0160	-0.0158	0.3544	0.0397
		P-value	0.001	0.001	<0.001	0.674
	ApoE ε4 carrier	β	-0.0523	0.0312	0.4528***	-0.1845
		b	-0.0147	0.0088	0.3775	-0.0621
		95% LCL	-0.0587,	-0.0380,	0.2653,	-0.1278,
		95% UCL	0.0293	0.0555	0.4897	0.0036
		P-value	0.514	0.713	<0.001	0.064
	Comparison	χ^2	0.88	3.19	2.14	3.31
		P-value	0.349	0.074	0.144	0.069
MSLS-CVRFS	ApoE ε4 noncarrier	β	-0.1309**	-0.1340**	0.3066***	0.0101
		b	-0.0807	-0.0826	0.6001	0.0032
		95% LCL	-0.1378,	-0.1419,	0.4207,	-0.0311,
		95% UCL	-0.0235	-0.0232	0.7795	0.0375
		P-value	0.006	0.006	<0.001	0.857
	ApoE ε4 carrier	β	-0.1248	-0.0683	0.4442***	-0.1273
		b	-0.0807	-0.0442	0.8569	-0.0427
		95% LCL	-0.1650,	-0.1414,	0.5614,	-0.1072,
		95% UCL	0.0035	0.0531	1.1525	0.0219
		P-value	0.060	0.373	<0.001	0.195
	Comparison	χ^2	0.00	0.44	2.09	1.55
		P-value	0.999	0.506	0.148	0.213

*P<0.050; **P<0.010; ***P<0.001.

4.5 Discussion

This research provides a comprehensive examination of arterial stiffness as a mediator of associations between modifiable CV risk and cognitive function in carriers and noncarriers of the ApoE ε4 allele. We found that arterial stiffness was a mediator of several important associations in ApoE ε4 carriers, but not noncarriers. No previous research has examined this mediation pathway to our knowledge. However, our findings are supported by several studies relating modifiable CV risk to arterial stiffness and arterial stiffness to cognitive function in adults with variable genetic risk.

The large arteries are rich in elastic tissue, allowing them to buffer pulsatile blood flow generated by the heart with each contraction and ensure continuous perfusion of systemic body tissue. (Hall, 2015) Elastic tissue is replaced with stiffer collagen fibers, calcium salts are deposited within the arterial walls and the endothelial cells that modulate vasomotor tone are damaged with advancing age and the aggregation of modifiable CV-RFs, such as uncontrolled systolic BP and fasting glucose. (Wen, et al., 2015; Prenner & Chirinos, 2015; Benetos, et al., 2002) Subsequent arterial stiffening increases blood flow pulsatility in smaller blood vessels and induces vascular alterations which limit oxygen delivery to the brain and cause cerebral small vessel diseases, including lacunar infarcts, cerebral microbleeds and white matter hyperintensities. (Mitchell, et al., 2011)

Consistent with these findings, cross-sectional and longitudinal associations between higher arterial stiffness and lower cognitive function are frequently observed, albeit primarily in studies utilizing limited neuropsychological test batteries. A full review of the literature linking arterial stiffness and cognition can be found in work by Qui and Fratiglioni (2015) and Iulita et al. (2018). Previous research also indicates that carriers

of the ApoE ε4 allele have worse cognitive function than noncarriers at fixed levels of modifiable CV risk (Bangen, et al., 2013; Knopman, Mosley, Catellier, & Coker, 2009) and arterial stiffness (Cambronero, et al., 2018). Physiological mechanisms underlying these associations are unclear, albeit investigators have hypothesized that ApoE ε4 carriers experience a weakened vascular state in which normal protective mechanisms are compromised due to neuropathology. As a result, brain pathologies emerge in carriers at levels of risk that are not harmful to noncarriers.

We found that arterial stiffness mediated several important associations between modifiable CV risk and cognitive function in ApoE ε4 carriers. Each 1 SD of higher systolic BP (21 mmHg) was associated with 0.36-0.38 SD higher PWV and PWV (3 m/s) with 0.19-0.24 SD lower Global Cognition, AR, VSOM, Naming, ST and VEM. Each 1 SD of higher fasting glucose (28 mg/dL) was associated with 0.24-0.25 SD higher PWV and PWV with 0.15-0.18 SD lower Global Cognition, AR, Naming and VC. Each 1 SD of higher HDL-C (17 mg/dL) was associated with 0.21 SD lower PWV and PWV with 0.16 SD lower Global Cognition. Lastly, each 1 SD of higher FRS (4 points) was associated with 0.45-0.46 SD higher PWV and PWV with 0.18-0.22 SD lower Global Cognition, VSOM, ST and VEM.

Although mediation was observed in ApoE ε4 carriers and not noncarriers, most mediation pathways did not significantly differ between groups when compared using χ^2 tests. Higher modifiable CV risk was a powerful predictor of higher arterial stiffness regardless of ApoE genotype and should be treated in primary care settings accordingly. However, higher arterial stiffness was only associated with lower cognitive function in ApoE ε4 carriers. Arterial stiffness is fairly easy and inexpensive to assess (Singer, Trollor, Baune, Sachdev, & Smith, 2014) and therapeutic strategies targeting BP,

inflammation, cholesterol and endothelin have been proposed to modulate stiffening processes (Iulita, Noriega de la Colina, & Girouard, 2018; Janić, Lunder, & Sabovič, 2014). With such strategies available, arterial stiffness could be an additional target for interventions designed to slow nonnormative cognitive aging, especially in ApoE ε4 carriers and adults with high modifiable CV risk.

Effect sizes reported in this research are small and short-term effects resulting from the treatment of high arterial stiffness would be limited for adults in primary care settings. However, nonnormative cognitive aging is progressive and small reductions in risk resulting from early treatment could have significant long-term implications at the population level. While additional research is conducted, physicians should educate their patients on the importance of maintaining CV health for promoting enhanced brain aging. (Qui & Fratiglioni, 2015)

4.5.1 Study Limitations

The pathophysiological mechanisms linking modifiable CV risk, arterial stiffness and longitudinal cognitive change are not fully understood. The MSLS did not include brain imaging, which would have provided us with the data needed to conduct an in-depth examination of these mechanisms. This research was cross-sectional in nature, which prevented us from establishing causality. Further research is needed in which modifiable CV risk, arterial stiffness and cognitive function are examined over time. Lastly, MSLS participants were well educated. As education increases cognitive reserve and protects against cognitive decline (Meng & D'Arcy, 2012), results presented in this research are conservative.

4.5.2 Study Strengths

The MSLS design permitted us to examine associations between modifiable CV risk, arterial stiffness and cognitive function in community-dwelling adults who were not selected for CVD or cognitive impairment. Key components of CV risk were also assessed and an extensive neuropsychological test battery used to index multiple cognitive domains was employed. To our knowledge, this is the first examination of arterial stiffness as a mediator of associations between modifiable CV risk and cognitive function in ApoE ε4 carriers and noncarriers.

4.6 Conclusion

Higher arterial stiffness was a mediator of associations between modifiable CV risk and cognitive function in carriers, but not noncarriers of the ApoE ε4 allele. Systolic BP, fasting glucose and FRS were positively associated with PWV, HDL-C was negatively associated with PWV and PWV was negatively associated with several domains of cognitive function. Further research is needed to confirm these findings and extend them longitudinally. Further research is also needed to develop effective interventions that slow nonnormative cognitive aging by treating modifiable CV-RFs and higher arterial stiffness, especially in ApoE ε4 carriers.

Chapter 5

CONCLUSION

The objectives of this research were to determine whether: 1. Aggregate CV risk and major modifiable CV-RFs are associated with cognitive function across adulthood and; 2. Arterial stiffness mediates these associations in adults with variable ApoE genotype. Three studies were performed to accomplish these objectives. Major findings, clinical implications and future research directions are discussed below.

5.1 Major Findings

Study 1 examined associations between 2 measures of aggregate CV risk and cognitive function across adulthood to determine whether such measures could be used to identify adults early in the nonnormative cognitive aging trajectory when intervention would be most effective. We found that higher FRS and MSLS-CVRFS were associated with lower function across multiple cognitive domains in cross-sectional, prospective and longitudinal analyses. A few associations for each measure became significant with advancing age, but most were observed at all ages.

Study 2 examined associations between 4 major modifiable CV-RFs and cognitive function across adulthood to determine what to target in interventions designed to slow cognitive decline. We found that higher systolic BP, diastolic BP and fasting glucose and lower HDL-C were associated with lower function across multiple cognitive domains in cross-sectional, prospective and longitudinal analyses. Associations for

systolic BP, diastolic BP and fasting glucose became significant with advancing age, while those for HDL-C were observed at all ages.

Study 3 examined arterial stiffness as a mediator of associations between 6 measures of modifiable CV risk and cognitive function in adults with variable ApoE genotype to determine whether arterial stiffness should be considered as an additional intervention target in populations with high genetic risk. We found that higher arterial stiffness mediated cross-sectional associations between higher modifiable CV risk and lower function across multiple cognitive domains in carriers, but not noncarriers of the ApoE ε4 allele. The mediating role of arterial stiffness was strongest in analyses where systolic BP, fasting glucose and FRS were examined as predictors.

5.2 Clinical Implications

Findings of this research have important implications for clinical practice and intervention development. Each measure of modifiable CV risk examined was associated with multiple cognitive domains and the majority of findings were significant using cross-sectional and prospective designs. Cognitive domains most affected by high modifiable CV risk were Global Cognition, VSOM and WM, each of which is vital for activities of daily living and impaired in adults with dementia, the hallmark of nonnormative cognitive aging. (Cooper & Greene, 2005; Lezak, Howieson, & Loring, 2004) Lowering modifiable CV risk could potentially slow decline in these and other important domains, helping adults maintain independence and lead longer, healthier lives.

5.2.1 Screening

The FRS and MSLS-CVRFS utilize data on similar modifiable CV-RFs obtained from medical history review, BP assessment and blood assays. Both measures

examined predicted lower function across multiple cognitive domains in this research. The MSLS-CVRFS is newer and has been examined in few studies compared with the FRS, but was found to be the superior measure, predicting lower function across every cognitive domain except for VEM in cross-sectional and prospective analyses. High arterial stiffness was found to mediate some of these associations in carriers but not noncarriers of the ApoE ε4 allele. Screening tools for the ApoE ε4 allele are currently being developed (Calero, García-Albert, Rodríguez-Martín, Veiga, & Calero, 2018) and could be used in conjunction with measures of aggregate CV risk to identify adults at risk for cognitive decline early in the nonnormative trajectory when intervention would be most effective. However, additional research is needed to confirm and extend these findings before screening protocols can be developed and implemented.

5.2.2 Treatment

Each modifiable CV-RF examined in this research was associated with cognitive function and is treatable. Current guidelines recommend lowering BP to <120/80 mmHg in adults with hypertension (Whelton, et al., 2018), maintaining a fasting glucose level between 80-130 mg/dL in adults with diabetes (American Diabetes Association, 2018) and raising HDL-C to >40 mg/dL in adults with dyslipidemia (Jellinger, et al., 2017) using a combination of medication and lifestyle changes. HDL-C was the best predictor of cognitive function at all ages in this research and should be strictly monitored and treated accordingly. Systolic BP, diastolic BP and fasting glucose also became strong predictors of cognitive function with advancing age. Efforts to monitor and treat these modifiable CV-RFs thus becomes increasingly important as individuals move through-out adulthood. In addition to slowing cognitive decline directly, lowering systolic BP

and fasting glucose could modulate arterial stiffening and associated cognitive changes in carriers of the ApoE ε4 allele.

Effect sizes reported in this research are small and short-term effects resulting from the treatment of modifiable CV-RFs based on current guidelines would be limited. However, nonnormative cognitive aging is progressive and small reductions in risk resulting from early treatment could have significant long-term implications at the population level. Additional research is needed to confirm and extend these findings, as well as determine the extent to which treatment of modifiable CV-RFs could slow cognitive decline, before effective interventions can be developed and implemented.

5.3 Future Research

The MSLS design permitted us to examine associations between modifiable CV risk and cognitive function using a sample of community-dwelling adults without major impairment at Wave 6 and Wave 7. Cross-sectional and prospective associations were abundant, while longitudinal associations were more limited. Follow-up time averaged 4.5 years and may not have been sufficient to adequately capture the cognitive decline characteristic of early nonnormative cognitive aging. Furthermore, the MSLS lacked the capacity to perform brain imaging and the physiological mechanisms underlying each association examined are unclear. Additional research employing longer follow-up time and brain imaging techniques is needed to strengthen our findings. As research is performed and interventions are developed, physicians are encouraged to educate their patients on the importance of maintaining CV health for promoting enhanced brain aging.

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