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Prospective Studies of Cardiovascular Risk Factors and Mild Cognitive Impairment

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PROSPECTIVE STUDIES OF CARDIOVASCULAR RISK FACTORS AND MILD COGNITIVE IMPAIRMENT

By

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A DISSERTATION

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An Abstract of the Dissertation Presented
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The association of cardiovascular risk factors including hypertension, diabetes, cholesterol, kidney function, and arterial stiffness with cognitive impairment in older adults is a well-studied phenomenon. However, there is considerably less evidence relating cardiovascular health specifically to a diagnosis of Mild Cognitive Impairment (MCI). As a precursor state of dementia, MCI is characterized by a decline in cognitive function from previous level, but not to the degree that activities of daily living are impaired. Not everyone who is diagnosed with MCI will eventually transition to dementia, but the transition rates are much higher compared to the general population (5-15% per year compared to 1-2%). The primary aim of the current investigation is to examine the relationship between individual cardiovascular risk factors and 5-year incident MCI risk and to investigate whether these relationships are moderated by apolipoprotein E genotype (APOE). An additional primary aim was to investigate whether an aggregation count of cardiovascular risk factors (MSLS-CVRFS) and two common cardiovascular risk factor profiles (FRS and ASCVD risk score) were related to 5-year incident MCI risk. Following exclusions for dementia, the study sample included 625 (Average baseline age: 61.98, 61% female) participants from the 6th and 7th waves

of the Maine-Syracuse Longitudinal Study (MSLS). MCI diagnosis was made by a team of three investigators applying established MCI diagnostic criteria, with 96 participants diagnosed with possible MCI. Multiple logistic regression analysis was used to examine the association between individual baseline cardiovascular risk factors (SBP, TC, HDL, LDL, TRIG, GFR, THCY, Diabetes, PWV) and MCI with adjustment for basic demographic covariates including age, sex, years of education, and ethnicity. The same method was used for determining APOE interaction effects and relating cardiovascular risk factor scores (CVRFS, FRS, ASCVD) with MCI risk. Among individual risk factors, higher GFR and HDL were associated with lower MCI risk, while diabetes was associated with higher MCI risk. No APOE interaction effects were observed. All three of the cardiovascular risk factor scores tested were associated with higher MCI risk. These findings have clinical implications with regard to predicting MCI risk with a combination of cardiovascular risk factors. While these factors have previously been related to continuously distributed cognitive performance measures, it is critical that their relationship to a clinically defined binary outcome like MCI be investigated because treatment decisions are based on diagnosis.

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LIST OF ABBREVIATIONS

Aβ	Beta amyloid
AD	Alzheimer's disease
ADL	activity of daily living
APOE	apolipoprotein E
ASCVD	arteriosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CHD	coronary heart disease
CIND	Cognitive Impairment, No Dementia
CKD	Chronic Kidney Disease
CN	cognitively normal
CRP	c-reactive protein
CSF	cerebrospinal fluid
CVD	cardiovascular disease
CVRFS	Cardiovascular Risk Factor Scale
DBP	diastolic blood pressure
DLB	Dementia with Lewy Bodies
FDG	flurodeoxyglucose
FRS	Framingham Risk Score
FTD	Frontotemporal Dementia
GFR	glomerular filtration rate

HDL	high density lipoprotein
HHCY	hyperhomocysteinemia
LDL	low density lipoprotein
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Exam
MRI	Magnetic Resonance Imaging
MSLS	Maine-Syracuse Longitudinal Study
PET	positron emission tomography
PWV	pulse wave velocity
SBP	systolic blood pressure
TC	total cholesterol
THCY	plasma total homocysteine
TRIG	triglycerides
WAIS-III	Wechsler Adult Intelligence Scale-III
WMH	white matter hyperintensity
WMS-R	Wechsler Memory Scale-Revised
VaD	Vascular dementia

1. INTRODUCTION

1.1. Normal Cognitive Aging

Cognitive changes with age are an expected component of the human lifespan. Therefore, it can be difficult to distinguish the pattern of change that can be considered "normal" from what can be considered abnormal or pathological in nature. The cognitive and functional deficiencies associated with dementia, be it Alzheimer's disease (AD) or Vascular Dementia (VaD), are obvious in comparison to a healthy older adult, but as efforts against dementia are increasingly directed towards preventing impairment in the first place this comparison is not as helpful anymore. It has become necessary to identify cognitive impairment of a pathological nature before extensive functional loss, and the concept of Mild Cognitive Impairment (MCI) has arisen to accomplish this. In order to investigate MCI, it is important to understand the type and degree of cognitive change that one can expect in a healthy, cognitively normal (CN) older adult.

The concept of crystallized vs fluid intelligence is often a featured component of what constitutes normal cognitive aging. Crystallized intelligence refers to long term memory related abilities including vocabulary, knowledge, and occupational expertise. Fluid intelligence relates more to short term and working memory related abilities including novel problem solving, information processing, and psychomotor abilities (Harada, Love, & Triebel, 2013; Anstey & Low, 2004). This distinction is often used to summarize normal cognitive aging as fluid intelligence is thought to peak around mid-30s whereas crystallized intelligence is thought to steadily increase throughout the lifespan into the 70s (Salthouse, 2012). While helpful, this distinction is somewhat simplistic, and the pattern of cognitive decline associated with successful aging free

from pathology is more complex and dependent on additional factors besides age alone.

Going beyond a simple distinction of crystallized vs fluid intelligence, a variety of changes are seen in cognition in normal aging. For declarative memory, episodic memory is expected to decline with age while semantic memory persists into late life (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). However, non-declarative memory, including procedural memory, remains largely unchanged across the lifespan (Lezak, Howieson, Bigler, & Tranel, 2012). These memory changes are consistent with other studies that have found acquisition (the ability to encode new information) and retrieval of recently learned information decline with age (Haaland, Price, & Larue, 2003; Harada et al., 2013; Price, Said, & Haaland, 2004) whereas retention of successfully learned information in long term memory is maintained (Whiting & Smith, 1997). Likewise, it is normal for older adults to decline in tasks involving selective and divided attention, although with simple attention tasks no impairment is seen (Salthouse, Fristoe, Lineweaver, & Coon, 1995). Reductions in processing speed and executive function are also normal, with older adults performing worse at tasks involving mental flexibility, response inhibition, inductive reasoning, and abstraction (Lezak et al., 2012; Singh-Manoux et al., 2012; Wecker, Kramer, Hallam, & Delis, 2005). A variety of other cognitive abilities are relatively preserved in normal aging including language skills and ability to understand similarities and proverbs (Harada et al., 2013). These changes in cognitive abilities refer to averages, but individual differences still play a large role in determining whether an individual will experience cognitive decline with age, and what degree of impairment will occur.

Often degree of impairment (whether normal or abnormal) is subject to individual differences in genetics, education, occupation, and culture. These factors, among others, have been bundled into a concept known as cognitive reserve, and higher cognitive reserve may be protective against deficits associated with normal aging and those associated with pathology (Stern, 2002). Education in particular has been recognized as an influential predictor of cognitive function in several recent normative value publications, including a study of centenarians who are of particular value to the study of cognitive aging (Davey et al., 2010; G.A. Dore, Elias, Robbins, Elias, & Brennan, 2007). Other experimental studies have reported an effect of education on age related cognitive impairment, but the effect may largely depend on the type of cognitive ability being measured (Ardila, Ostrosky-Solis, Rosselli, & Gómez, 2000).

In addition to cognitive performance changes there are identifiable structural brain differences in normal aging vs abnormal cognitive aging that may play a causal role in observed deficits. For example, hippocampal atrophy is traditionally associated with AD, but still occurs in normal aging to a much smaller extent (De Leon et al., 1997). Early studies of structural changes in the aging brain likely overestimated the extent of neuronal death, with the current thought being that subtle changes involving neuron size and synaptic plasticity in key cortical areas may relate to cognitive changes (Morrison & Hof, 1997; Terry & Katzman, 2001; Whalley, Deary, Appleton, & Starr, 2004). Reductions in gray matter have been reported as early as age in the 20s (Terry & Katzman, 2001). The concept of cognitive reserve is supported with structural evidence as well, suggesting it may contribute to neural plasticity, larger brain size, and reduced neural activity during cognitive tasks, possibly reflecting more efficient resource usage

(Solé-Padullés et al., 2009; Whalley et al., 2004). These small structural changes and subtle loss of general efficiency among key brain circuits are in sharp contrast to the biological changes seen in dementia (See Section 1.3.3.). For further reading regarding cognitive aging and accompanying structural changes consult the following resources (Park, Denise c.; Reuter-Lorenz, 2012; Raz & Rodrigue, 2006; Salthouse, 1991).

Ultimately, separating normal cognitive aging from pathological cognitive changes can be difficult. However, the changes observed with normal aging are not comparable to pathological conditions such as dementia, which includes crippling deficiencies in cognitive function and ability to perform activities of daily living (ADLs). Normal changes in cognitive function do not compare to even mild degrees of dementia (Erkinjuntti, Laaksonen, Sulkava, Syrjalainen, & Palo, 1986). While there are cognitive deficits seen in normal cognitive aging, they are of a minor degree and not enough to interfere with daily function or social involvement. The idea of pathology with respect to cognitive aging should be based on the degree to which the changes interfere with an individual's ability to function independently. However, in terms of dementia this introduces a problem. With treatment for dementia increasingly focused on identifying prodromal states, it has become necessary to distinguish normal cognitive aging from abnormal aging without relying on overt functional impairment in an effort to diagnosis and label this prodromal condition. The clinically defined concept of MCI has arisen to achieve this, and it represents a likely transitional phase between normal cognition and dementia. This pathway between CN, MCI, and Dementia does not exist on the normal continuum for cognitive changes with advancing age but rather represents a separate

pathway of pathological changes far exceeding those seen in normal aging (See Figure 1.).

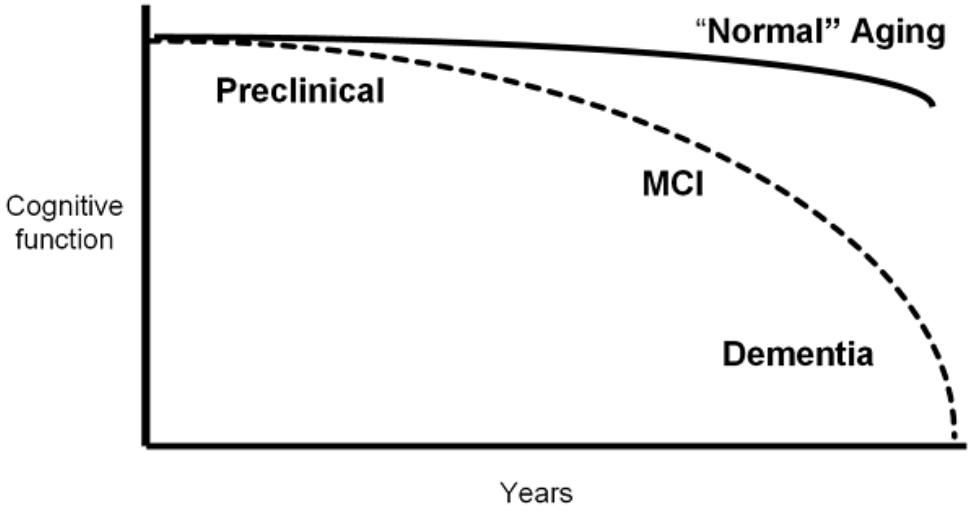

Figure 1. Time Course of Dementia with Preclinical MCI Phase
Note. While some decline in cognitive function is expected with increasing age, the changes seen in MCI/Dementia pathology are of a much more significant degree. (Sperling et al., 2011)

It is of chief epidemiological importance to determine what factors might influence whether an individual remains CN with advancing age or diverges to a more sinister degree of cognitive impairment, potentially indicative of underlying dementia pathology. The current study is focused on the role of cardiovascular risk factors in this divergence by focusing on MCI risk. The rationale for this objective is based on the overwhelming evidence that cardiovascular risk factors are associated with cognitive performance in older age. Therefore, before discussing the conditions of dementia and MCI, and how they may relate to cardiovascular health, in the next section we will summarize findings suggesting an association between cardiovascular risk factors and cognition assessed on a continuum.

1.2. Cardiovascular Risk Factors and Cognitive Functioning

1.2.1. Hypertension

The relationship between blood pressure and cognitive functioning has been studied extensively, often with conflicting results until the latter half of the 20th century. At this time, longitudinal studies began to consistently present evidence associating high blood pressure at mid-life with a decline of cognitive functioning in older age (M.F. Elias, Goodell, & Dore, 2012; M.F. Elias, Wolf, D'Agostino, Cobb, & White, 1993; Wilkie & Eisdorfer, 1971). More recent studies have specifically shown an association between elevated midlife blood pressure and increased risk of dementia (Alonso et al., 2009; Korf, White, Scheltens, & Launer, 2004; Qiu, Winblad, & Fratiglioni, 2005).

1.2.2. Arterial Stiffness

Arteriosclerosis is the progressive hardening of arteries due to age or pathological processes such as plaque buildup along the arterial wall (atherosclerosis). Compliant arteries are necessary for optimal hemodynamics, allowing the heart to supply the body with oxygenated blood with as little impetus as possible (Berne & Levy, 1986). Stiff arteries reduce this efficiency and create strain on the heart and peripheral capillary beds, as well as increasing the risk of thrombosis, emboli, and infarction. Severe atherosclerosis is associated with an increased dementia risk and may be exacerbated by the Apolipoprotein E ε4 (APOE) allele, discussed further in Section 1.2.7 (Hofman et al., 1997; Laurin, Masaki, White, & Launer, 2007; van Oijen et al., 2007). Pulse Wave Velocity (PWV; meters/second) is a recently developed indirect measure of arterial stiffness using applanation tonometry that measures the speed of the pressure wave generated by heart systole as it travels to the periphery and is

reflected back. Several recent studies have associated increased PWV (which reflects stiffer arteries) with a decrease in cognitive functioning (M.F. Elias et al., 2009; Wendell, Zonderman, Metter, Najjar, & Waldstein, 2009).

1.2.3. Homocysteine

Homocysteine is an amino acid normally metabolized by methionine and is measured in plasma total homocysteine (tHcy; μmol/L). A high level of tHcy, known as hyperhomocysteinemia (HHcy) can cause endothelial cell damage and inflammation, gradually deteriorating or hardening blood vessel walls in an arteriosclerotic process (Obeid & Herrmann, 2006). Homocysteine levels are heavily influenced by diet choices, and diets low in vitamin B6, vitamin B12, folic acid and high in methionine (animal proteins) are risk factors for HHcy, as is older age and male sex (Kalra, 2004). The inflammatory properties of homocysteine form the basis for the pathology of HHcy as it pertains to brain health and dementia. Homocysteine promotes neuronal degeneration, particularly of white matter, a consistent target of cerebrovascular pathologies (Obeid & Herrmann, 2006). Results from the Framingham Heart Study suggest that individuals with a tHcy level over 14 μmol/L have twice the risk of developing Alzheimer's disease, and associate HHcy with smaller brain volume and silent infarctions (Seshadri et al., 2002, 2008). Numerous other studies have associated elevated levels of tHcy with increased dementia risk (Ho et al., 2011; van Dam & van Gool, 2009; Wald, Kasturiratne, & Simmonds, 2011).

1.2.4. Cholesterol

The relationship between cognitive function and serum lipid levels including Total Cholesterol (TC; mmHg), High density lipoprotein (HDL; mmHg), Low density

lipoprotein, (LDL; mmHg), and triglycerides (TRIG; mmHg) is controversial. Many studies have positively associated TC with cognitive function while others have found a negative association. HDL is considered to be a positive factor, whereas TRIG is considered to be a negative factor, but results are mixed on these lipid levels as well. For a full review of this topic consult (Muldoon & Conklin, 2014).

1.2.5. Diabetes

Diabetes mellitus is a significant risk factor for cognitive impairment, and has several common cardiovascular comorbidities which can also impair performance (Awad, Gagnon, & Messier, 2004; Rodstein, 2001). Commonly affected cognitive abilities include attention, memory, processing speed, and executive functioning (Kodl & Seaquist, 2008). Further reading on this extensively studied topic is available in several recent reviews (Biessels, Deary, & Ryan, 2008; Brands, van den Berg, Biessels, & Kessels, 2014).

1.2.6. Renal Function

Renal function is a reflection of kidney health and can be represented numerically by glomerular filtration rate (GFR), the rate of blood flow through the kidney. GFR is estimated through various formulae usually including serum creatinine (a metabolic byproduct removed from the blood by the kidneys), age, sex, ethnicity, height, and weight. A sustained GFR of less than 60 mL/min is usually a cut-off associated with chronic kidney disease (CKD), which has been negatively associated with cognitive function in early and late stages of CKD (Brady et al., 2009; Elias et al., 2009). Kidney function is usually dichotomized into CKD or non-CKD based on GFR cut-offs when

studied in association with cognitive function (Buchman et al., 2009; Elias et al., 2009; Kurella-tamura et al., 2009).

1.2.7. Apolipoprotein E Genotype

Apolipoprotein E (APOE) is a metabolic protein linked to cognitive impairment based on the alleles of the corresponding chromosome 19 gene APOE. Specifically, the presence of at least one ε4 allele (APOE ε4 carrier) is a risk factor for cardiovascular disease, dementia, and impaired cognitive function (Farrer et al., 1997; Small, Rosnick, Fratiglioni, & Bäckman, 2004). APOE ε4 carrier status has also been shown to interact with other risk factors, including diabetes, potentially exacerbating cognitive impairment (G. A. Dore, Elias, Robbins, Elias, & Nagy, 2009; M. N. Haan, Shemanski, Jagust, Manolio, & Kuller, 1999). Aside from considering APOE genotype a risk factor for cognitive impairment, its interaction with other cardiovascular risk factors needs to be considered.

1.3. Dementia

1.3.1. Overview

Dementia can refer to a large number of debilitating diseases that can compromise an individual's cognitive functioning, personality, social functioning, and ability to live independently. It is a highly heterogeneous condition resulting from several different pathologies, and most often combinations of pathologies. While the most common form is presumed to be Alzheimer's disease (AD), other forms include Vascular Dementia (VaD), Dementia with Lewy Bodies (DLB), Frontotemporal Dementia (FTD). Dementia can be accompanied by a variety of comorbidities including Parkinson's disease and Huntington's disease. As worldwide life expectancies get

longer, these aging-related diseases have been increasing in prevalence and are quickly becoming a leading healthcare crisis in the 21st century. Almost 50 million people worldwide are estimated to have some form of dementia, with a projected 8 million new cases each year (World Health Organization). In 2010 worldwide dementia costs were estimated to be $604 billion, about 1% of world gross domestic product, an enormous cost considering prevalence rates are expected to triple by 2050 (World Health Organization). This increase in dementia prevalence will have devastating social and economic repercussions, and considering the lack of effective treatment or prevention techniques requires immediate attention as a worldwide research priority.

1.3.2. Diagnosis

Diagnosing dementia usually involves detecting a clinically significant decline in cognitive function from a previous level, to the extent that the patient can no longer function independently or perform activities of daily living (ADLs; getting dressed, personal hygiene, going shopping etc.). While episodic memory impairment is a common cognitive deficit, particularly in the early stages of AD, other deficits in cognitive domains including language, attention, executive functioning, working memory, and visual-spatial reasoning are possible. Biomarkers and neuropathology are becoming an increasingly important part of any dementia diagnosis, taking into account the variety of etiologies responsible for the condition. For example, detection of amyloid markers in the brain or cerebrospinal fluid (CSF) is now an important diagnostic aspect of AD, while cerebrovascular disease or the presence of cerebrovascular risk factors is a required part of most VaD diagnoses. Other dementia pathologies such as DLB and FTD are different and can result in various clinical phenotypes, but will not be discussed

in this study. Mixed etiologies are probably the most common cause of dementia, as vascular insults and vascular cascade have been shown to accompany AD pathology, resulting in patients exhibiting deficits characteristic of both AD and VaD (Jellinger & Attems, 2007; D. S. Knopman, 2006).

1.3.3. Pathology

1.3.3.1. Alzheimer's Pathology

Alzheimer's pathology is relatively well documented and consistent across cases with a general worsening of symptoms and pathology from onset until death. The two hallmark signs of the disease are intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein (a microtubule associated protein) and extracellular neuritic plaques formed by depositions of beta amyloid (Aβ). Neuronal atrophy is also common, particularly in the medial and temporal lobes, including the hippocampus. These regions are often the first affected by AD pathology and are likely associated with primary memory deficits in AD patients. As the disease progresses these pathologies can spread to other regions such as the frontal cortex, and cognitive functioning progressively worsens as a result of widespread synaptic death.

While a causal role for any of these biomarkers has yet to be established, their presence has become an integral factor in the diagnosis of AD, particularly amyloid plaques, which are required for diagnosis. Traditionally this has resulted in tiers of AD diagnosis denoted as possible, probable, and definite, the latter only possible with post-mortem evidence of AD pathology at autopsy. However, improved AD biomarker detection via neuroimaging and spinal taps for cerebrospinal fluid (CSF) have aided pre-mortem diagnoses. Magnetic-Resonance-Imaging (MRI) is useful for detecting areas of

structural atrophy. Positron emission tomography (PET) has proven invaluable in the detection of AD brain pathology. PET scans using Pittsburgh compound B (PiB) reliably detect amyloid plaque deposits in a full brain scan. Fluorodeoxyglucose (FDG) PET scans assess glucose metabolism across the brain, and can be used to check for hypometabolism in certain areas, particularly the medial and temporal lobes when assessing AD pathology.

1.3.3.2. Vascular Pathology

Vascular Dementia pathology is considerably more heterogeneous than AD pathology because it can be caused by any combination of cerebrovascular diseases with varying severity. Consequently, symptoms and prognosis can be more varied depending on the location and severity of the vascular insult. Stroke is perhaps the most obvious cerebrovascular event that could contribute to cognitive impairments of a dementia degree. However, other smaller vessel diseases are possible and over time can be just as impactful. Small vessel diseases are estimated to have a causal role in 40-70% of VaD cases (Román, 2003). These include lacunar infarctions (which are often asymptomatic), cerebral microbleeds, and leukoaraiosis. Small infarctions are localized tissue death due to an obstruction of normal blood flow to the area and are not necessarily uncommon. The prevalence of silent infarctions is about 20% in the normal population but as high as 50% in those with vascular disease (Longstreth et al., 2005). Silent infarctions are associated with a doubled risk of vascular cognitive impairment or dementia over a five year period (Longstreth et al., 2005). Leukoaraiosis is represented by white matter hyperintensities (WMH) on T2 weighted MRI images demonstrating the destruction of white matter tracts in the brain. This white matter damage is thought to be

associated with vascular mechanisms and is associated with typical cardiovascular risk factors including hypertension and diabetes, and may play a causal role in cognitive deficits seen in VaD.

1.3.3.3. Mixed Pathology

Dementia and MCI rarely fit into neat diagnostic paradigms perfectly describing the underlying pathology. The prevalence of mixed pathology both in dementia and MCI has been increasingly recognized, with some studies claiming a mix of AD and vascular pathology may account for the near-majority of dementia cases at around 40% (Price, Nguyen, Lamar, & Libon 2015; Lockhart and DeCarli 2015). VaD and AD pathology have considerable co-occurrence, with some going so far as to claim “Pure VaD” and “Pure AD” as rare (Jellinger & Attems, 2007). There is often a vascular component to AD, and unfortunately the two pathologies have a “complementary and synergistic relationship in the genesis of cognitive impairment” (D. S. Knopman, 2006). Growing evidence suggests that AD and vascular pathology may be additive in that individuals with mild AD or cerebrovascular pathology are less likely to progress to dementia than individuals with both (Fotuhi, Hachinski, & Whitehouse, 2009; Nagy et al., 1997; Schneider, Arvanitakis, Bang, & Bennett, 2007; Snowdon et al., 1997; Viswanathan, Rocca, & Tzourio, 2009).

The degree to which dementia varies in terms of mixed etiologies is not surprising considering that AD and VaD share several common risk factors, including cardiovascular risk factors. Mixed pathologies complicate differential dementia diagnosis because the brain areas effected can vary considerably from the common parietal-temporal damage seen in AD to the subcortical white matter damage often

observed in VaD. This may be the case for MCI diagnosis as well if this condition truly reflects early stages of the pathology seen in fully developed dementia. Cardiovascular risk factors may contribute to both AD and VaD pathology and both of these etiologies need to be considered when discussing preventive interventions and post-diagnosis treatments.

1.3.4. Prodromal State

Current efforts regarding the treatment of dementia are increasingly focused on prevention. This emphasis has resulted in increased attention to identifying prodromal states of dementia. While many states have been proposed and defined, the concept of MCI has emerged as an important clinical state in the progression of dementia pathology. MCI is an age associated decline in cognitive functioning from normal levels that does not meet thresholds for dementia diagnosis, nor impair the individual's daily functioning. While diagnoses and operational definitions for MCI vary, all agree that MCI is a clinically relevant category of cognition that represents a risk factor for progression to dementia. Identifying individuals presenting with MCI provides an opportunity for early preventative interventions to slow the progression to dementia or ideally stop it altogether, though a delay in transfer from MCI to dementia is the most realistic treatment outcome at this time. MCI will be discussed fully in the following section. While this study does not deal with intervention it does deal with MCI as primary cognitive outcome variable.

1.4. Mild Cognitive Impairment

1.4.1. Conceptual Overview

MCI is a continually developing clinical concept intended to represent a transitional period between normal cognitive functioning with age and dementia states. *Figure 1.* illustrates this concept as a transitional period between normal function and dementia, with a preclinical period predating the onset of MCI (Sperling et al., 2011). The concept originates from early longitudinal studies on aging and dementia, in which large groups of subjects appeared to fit in intermediate stages that could not be defined as normal or demented (Petersen, 2004). From a modern perspective this degree of impairment was originally defined as an intermediate stage of impairment based on the Global Deterioration Scale (Reisberg, Ferris, De Leon, & Crook, 1988). From this point, the concept has evolved under several names including benign senescence forgetfulness, age-associated memory impairment (AAMI), age-associated cognitive decline (AACD) and cognitive impairment no Dementia (CIND), although there has been considerable overlap between all of these systems of description and diagnosis (R. C. Petersen, 2004). The important and widely agreed upon characteristics of MCI are as follows: 1.) Person has an impairment in one or more cognitive domains that reflects a decline from previous function, 2.) Person has largely preserved independence and every day functioning and can perform activities of daily living (ADL) with little to no assistance, 3.) Person is not demented. How these characteristics are defined and measured, in addition to whether or not requiring corroboration by an informant (typically a family member), varies considerably. Moreover, meeting criterion two eliminates the possibility of meeting criterion 3 in most of these systematic approaches.

MCI represents a subtle continuum between what is considered normal cognitive aging and pathological impairment due to dementia, and this creates what is referred to as an ambiguous ‘grey zone’ with considerable overlap on either side of the continuum (Feldman & Jacova, 2005; Petersen, Smith, & Waring, 1999). See Figure 2. for a representation of this continuum and note the overlap on both sides of the period commonly defined as ‘MCI’. The lack of clinical consensus in the field for defining this period comes from several different sources, including but not limited to varying diagnostic tools such as cognitive assessment measures, differences in populations (e.g., community-based samples vs clinic referral samples), and perhaps most of all the several etiologies and pathology proposed to be behind MCI, which may vary as much as dementia etiology does (Petersen et al., 2014; Stephan et al., 2012). This has led to considerable variability in diagnosis and conceptualization of this important clinical period.

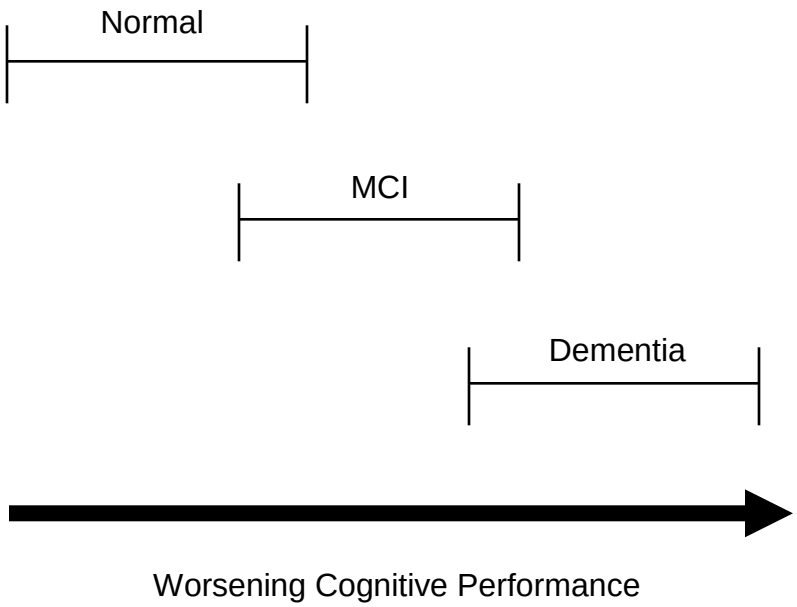

Figure 2. Continuum of Cognitive Performance from Normal to MCI to Dementia

1.4.2. Diagnosis

Diagnostic criteria for MCI have evolved via several nuanced changes and categorizations over the past two decades, but the fundamental Mayo Clinic criteria laid out by Petersen et al. in 2004 are still essential. Petersen laid out 5 defining characteristics of MCI, and while these are adjusted somewhat by other diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), National Institute on Aging-Alzheimer's Association (NIA-AA) etc.) the general principles are largely the same. These original criteria are outlined in Table 1., along with recent revised criteria. One may note that these criteria are focused specifically on memory impairment as this was thought to be the most common form of MCI, and the form most likely to predict AD (Petersen et al., 2014). These criteria are still relevant today but now represent a common MCI subtype referred to as Amnestic MCI or a-MCI (Petersen et al., 2014; Petersen, 2011).

Table 1. Mayo Clinic MCI Criteria Original and Expanded

Criteria	Original Mayo Clinic	Revised/ Expanded
Reported Memory Impairment (Self or Informant)	✓	
Reported Cognitive Impairment (Self or Informant)		✓
Objective Memory Impairment (Neuropsychological testing)	✓	
Objective Cognitive Impairment (Neuropsychological testing)		✓
Preserved general cognitive function	✓	
Preserved functional independence and ADLs	✓	✓
No dementia	✓	✓

The biggest shift in MCI diagnosis in recent years has been the adoption of multiple subtypes of MCI to reflect the variety of clinical phenotypes commonly seen. Diagnostic criteria have accounted for this by specifying the term 'cognitive impairment',

with more sensitivity to type of impairment, primarily involving memory or not. Revised Mayo criteria, in addition to NIA-AA criteria for MCI and DSM-V criteria for Mild Neurocognitive Disorder (NCD), now allow for cognitive impairment to reflect any cognitive domain, not just memory impairment (Petersen et al., 2014; Petersen, 2011). In recognition that multiple cognitive domains can be impaired in the same case, four major MCI subtypes have arisen to reflect different cognitive profiles. The four subtypes reflect two values: whether or not the individual has a memory impairment (amnestic or non-amnestic) and whether or not the individual has impairment in multiple cognitive domains (single domain or multi-domain). Therefore the current MCI subtypes are amnestic MCI single domain, amnestic MCI multi-domain, non-amnestic MCI single domain, and non-amnestic MCI multi-domain. Reliable prevalence rates for these subtypes have not been established at this time, though non-amnestic single domain MCI is considered rare (Petersen, 2004). It is important to recognize that these MCI subtypes do not reliably represent etiology of the condition and pertain only to clinical phenotype. The various brain pathologies though to be responsible for MCI and dementia have not been accurately mapped on to these diagnoses, though there is growing evidence that amnestic forms of MCI may be associated with AD pathology whereas non-amnestic forms may represent non-AD dementia pathologies including cerebrovascular disease (Feldman & Jacova, 2005; R. Petersen, Thomas, & M, 2005; Stephan et al., 2012).

While the essential aspects of cognitive impairment in MCI are becoming more established, there is little consensus in the field regarding specific tests or assessments, as well as corresponding cut-off scores, for use in diagnosing MCI. Larger scale

neuropsychological batteries provide a detailed cognitive profile of patients, but are not always practical to use in a clinical setting. Quicker assessments are often used, and even amongst these there is great variability in the specific tests used. Common assessments used include the Wechsler Adult Intelligence Scale Revised (WAIS-R), Wechsler Memory Scale-Revised (WMS-R), The Auditory Verbal Learning Test, The Wide Range Achievement Test (WRAT), Controlled Oral Word Associations, and the Boston Naming Test. Shorter assessments include the Mini Mental State Exam (MMSE) and the Montreal Cognitive Assessment (MOCA), though the MMSE has been criticized as not being sensitive enough as a single use measure detecting impairment. Studies often use multiple measures to attempt to detect impairment in multiple domains of cognitive functioning including memory, executive functioning, attention, language, and visuospatial ability. While no specific cutoff scores are agreed upon, it is generally considered that impairments ranging from .5-1.5 standard deviation units below age-based cognitively healthy norms are a good starting point, reflecting performance in the 31st percentile and lower (Petersen, 2003). However, impairment has to be examined considering previous function of the individual, which is more important than arbitrary cut-off scores. A change in function is a reliable indicator of possible MCI, and this approach is often used in epidemiological studies and retrospective analyses.

1.4.3 Prevalence and Incidence

Population statistics for MCI are difficult to determine given the variety of acceptable diagnostic criteria for clinical deficit or change from a previous level, and the population from which the individuals were sampled. Early epidemiological studies likely underestimated the prevalence of MCI in the population because of the memory bias in

diagnosis (Petersen et al., 2014). When MCI is rightfully conceptualized as including all forms of cognitive impairment prevalence statistics have been higher. In United States samples the prevalence of MCI in the 65+ year old population tends to range between 15-25% (Ganguli et al., 2010; O. Lopez, Jagust, & DeKosky, 2003; Manly et al., 2008; R. Petersen, Roberts, & Knopman, 2010; Plassman, Langa, & Fisher, 2008; Purser, Fillenbaum, Pieper, & Wallace, 2005). A reliable incidence rate is similarly challenging but some aggregate data suggests the rate may range between 20-70 per 1000 person-years (Petersen et al., 2014; Ward, Arrighi, Michels, & Cedarbaum, 2012). Despite the variability in statistics it is clear that MCI is not a rare condition and deserves attention.

1.4.4. Prognosis and Treatment

The clinical relevance of MCI depends on its use as a detection of a prodromal dementia state that provides the opportunity for early interventions and identification of at-risk populations. It is important to note that the prodromal state where MCI is first seen is part of the long latency period for dementia, where pathology is emerging in the brain but the individual is not yet demented as illustrated in Figure 3. (Sperling et al., 2011). Regardless of the various definitions and diagnostic procedures, MCI does reliably predict an increased risk of dementia as compared to normal cognitive aging. MCI is a risk factor for dementia, as it is now clear that lowered cognitive functioning in a number of domains predicts dementia many years later. Conversion rates from MCI to dementia vary, but are reported around 5-15% per year (Larrieu et al., 2002; Petersen et al., 1999; Petersen, 2011). This rate can be compared to an estimated dementia conversion rate of 1-2% per year from the general population (Petersen, 2011). Overall, several longitudinal studies have supported that MCI is a significant risk factor for

dementia and predicts a higher conversion rate, though not everyone with MCI will end up progressing to dementia (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006a; O. Lopez et al., 2003; Manly et al., 2008; Plassman et al., 2008). Some studies have shown reversal of MCI patients to cognitively normal levels at a rate as high as 40%, which likely reflects errors related to diagnosis being heavily memory-based in earlier approaches and the difficulty of separating normal cognitive aging from MCI (Larrieu et al., 2002).

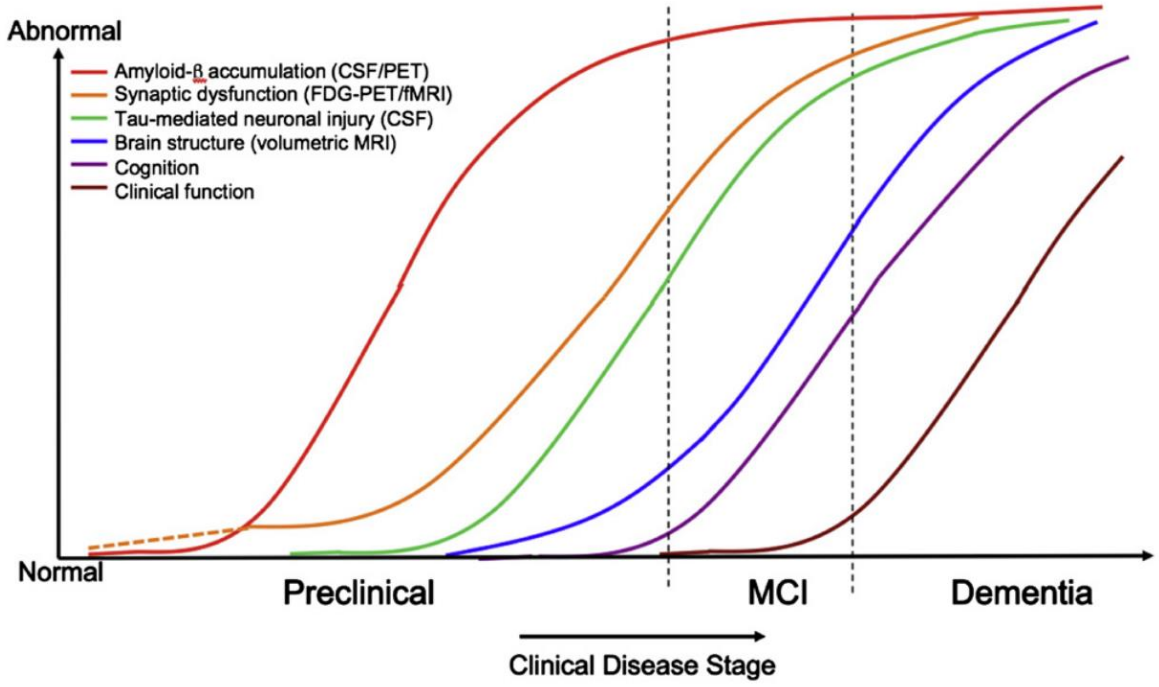

Figure 3. Neuropathological Cascade Preceding MCI and Dementia
Note. The prodromal phase of dementia is a long and dormant process of which MCI is the first phase in which cognitive deficits are observable. This example from (Sperling et al., 2011) provides a hypothetical model of AD pathology predating MCI and Dementia, likely by many years.

Several factors have been studied predicting higher risk of transitioning from MCI to dementia. The greater the extent of cognitive impairment of the individual the more rapid progression to dementia tends to be (Dickerson, Sperling, Hyman, Albert, & Blacker, 2007; Visser, Verhey, & Knol, 2009). The APOE ε4 allele has also been

associated with more rapid progression to dementia (Hsiung, Sadovnick, & Feldman, 2004; Mosconi et al., 2004). Neuroimaging has supplemented MCI to dementia transition risk assessment, but there are conflicting findings. A 2010 study by Jack et al. revealed that MCI subjects in the bottom 25% of hippocampal volume (revealed by MRI) for sex and age norms had a more rapid progression to dementia. Other AD biomarkers and neuropathology have been associated with transition from MCI to AD, including hypometabolism in the temporal and parietal lobes on FDG-PET scans (Chetelat et al., 2003; Drzezga, Grimmer, & Rjemenschneider, 2005; Landau, Harvey, & Madison, 2010). Cerebrospinal fluid markers of low beta amyloid peptide 42 and tau protein have similarly been shown to predict more rapid transition (Hansson et al., 2006), though amyloid has been found in cognitively healthy adults (DS Knopman, Parisi, & Salviati, 2003). The neuropathology of MCI is not well understood at this time, though there is some evidence that it may reflect early dementia pathology, which varies widely in etiology given the several different forms of dementia (Stephan et al., 2012).

Treatment for MCI is currently suboptimal, and pharmacological interventions have been challenging given the heterogeneity of the condition. At this time there is no FDA approved treatment for MCI (Petersen, 2011). A few clinical trials have taken place with largely null results. Donezpil, a cholinesterase inhibitor, failed to reverse cognitive decline in an MCI population (Russ & Morling, 2012) and similar results were observed for vitamin E trials (Farina, Isaac, Clark, Rusted, & Tabet, 2012; Petersen et al., 2014). Cognitive training has shown limited efficacy but may be a promising avenue for further trials (Jean, Bergeron, Thivierge, & Simard, 2010; Massoud, Belleville, & Bergman, 2007). While modification of cardiovascular risk factors has received mixed results in

terms of slowing the progression from MCI to Dementia (Di Carlo, Lamassa, & Baldereschi, 2007), there is some evidence that regular aerobic exercise can slow the progression significantly (Ahlskog, Geda, Graff-Radford, & Petersen, 2011). Ultimately, more clinical trials are necessary, ideally those that combine multiple interventions such as cognitive training, healthy lifestyle changes, and medication that are based on as much information as possible regarding the etiology of an individual's MCI.

1.5. Cardiovascular Risk Factors and MCI

The relationship between cardiovascular risk factors and cognitive functioning is well known as a result of a rich literature base (See Section 1.2.). However, the literature base associating cardiovascular risk factors with MCI specifically is much sparser. While MCI may be seen as an obvious corollary of continuous cognitive function, this important diagnostic entity requires more focused studies in order to determine the contribution of cardiovascular risk factors to a clinically defined condition of cognitive impairment. Table 2. summarizes some of the most well-cited studies in this small but developing literature base. These studies vary in design and follow-up periods, but all attempted to associate cardiovascular risk factors with MCI specifically, and not continuous cognitive function. To date, the risk factors studied include hypertension, coronary artery disease (CAD), stroke, Type II Diabetes, Total Cholesterol (TC), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Triglycerides (TRIG), HCY, APOE Genotype, and vascular brain damage in the form of white matter lesions, infarcts, and atrophy.

Table 2. Review of Cardiovascular Risk Factors for MCI

Study	Design	Risk Factor(s)	Results
(Solfrizzi et al., 2004)	Prospective	Hypertension, CAD, Stroke, Type 2 Diabetes, TC, HDL	CV Risk factors likely increase the risk of MCI progression to dementia, but did not find that these factors predict higher MCI risk
(Cheng et al., 2012)	Meta-Analysis	Type 2 Diabetes	Higher incidence of MCI in subjects with Diabetes
(J. A. Luchsinger et al., 2007)	Prospective	Type 2 Diabetes	Diabetes predicts MCI prospectively
(Faux et al., 2011)	Cross-Sectional	Homocysteine	Hcy did not relate to MCI
(Kim et al., 2007)	Cross-Sectional	Homocysteine	Hyperhomocysteinemia linked to MCI in an older cohort
(M Kivipelto et al., 2001)	Prospective	Hypertension, TC, Antihypertensive medication, Type 2 Diabetes	Midlife SBP and TC predicted MCI, diabetes and antihypertensive meds did not
(O. L. Lopez et al., 2003)	Prospective	Hypertension, APOE, Vascular brain damage (MRI), Stroke, Type 2 Diabetes, Heart Disease	Hypertension, APOE genotype, MRI evidence of white matter lesions/infarcts, diabetes, and heart disease all predicted MCI prospectively. Stroke did not predict MCI.
(Rasquin et al., 2004)	Prospective	Stroke	Stroke predicted MCI at one year follow up but evidence this impairment may be reversible
(Reitz et al., 2007)	Prospective	Hypertension, APOE	Hypertension predicted 5 year all cause MCI and non-amnestic MCI, but not amnestic MCI. No interaction with APOE genotype.
(Reitz et al., 2008)	Prospective	TC, HDL, LDL, TRIG, Lipid-lowering treatments	No relationship between serum lipid levels and MCI, no effect of lipid-lowering treatments on MCI risk
(Toro et al., 2014)	Prospective	TC, APOE	Higher TC predicted MCI over 14 year time period but did not interact with APOE
(D. et al., 2010)	Cross sectional	TC (Familial Hypercholesterolemia), APOE	Familial hypercholesterolemia associated with MCI, independent of APOE genotype

At present, results associating these risk factors with MCI are somewhat mixed. A few of the major studies demonstrated an association between common cardiovascular risk factors like hypertension, diabetes, and lipid levels on MCI, but others reported no association. Some of these inconsistencies are likely due to differences in MCI diagnosis. The literature base is strong enough to warrant further study, both in the interest of replication and new hypotheses. There are many gaps in the cardiovascular risk factor and MCI framework that can be addressed. No studies associating PWV measured arterial stiffness or GFR measured renal function with MCI were found. Homocysteine studies have been done and while informative they are mostly cross-sectional, resulting in an obvious need for a prospective study of HCY and MCI. Furthermore, while APOE genotype has been studied there is a need for more testing of interactions between APOE genotype and cardiovascular risk factors. This gap coincides with an overall lack of studies that associate the aggregation of multiple cardiovascular risk factors, and how they may interact to contribute to MCI risk. This study will attempt to address some of the gaps in this literature, as well as replicate other findings.

1.6. Cardiovascular Risk Factor Scales

1.6.1. Cardiovascular Risk Prediction Models

It is now well known that the combination of multiple cardiovascular risk factors can aggregate and contribute to CVD risk (Goff et al., 2014; Piepoli et al., 2016; Yusuf et al., 2004). However, it can be difficult to quantify exact risk for a patient who visits his or her clinician with a handful of risk factors, some of which may not reach clinically established “cut-offs” for what constitutes risk. In an effort to make risk calculation

easier for individual patients, various groups from large epidemiological studies on cardiovascular health have devised risk models using Cox Regression hazards models in order to identify variables and their individual contribution to risk. Because these studies are focused on cardiovascular health, the outcome "event" being predicted by these models is usually some degree of first time CVD or specifically first time Coronary Heart Disease (CHD). These models are constantly evolving to incorporate new risk variables and more data from larger study populations, but there is an emphasis on keeping the models as simple as possible for use in a clinic setting to quickly quantify a patient's 10 year risk of CVD/CHD.

The basic foundation for many of these cardiovascular risk prediction models comes from early attempts by the Framingham Heart Study to quantify CVD Risk (Kannel, McGee, & Gordon, 1976). Framingham's General Cardiovascular Risk score has since been refined with additional decades worth of data, and has now been adopted to a simple point scoring system that incorporates age, sex, SBP, hypertensive medication treatment, TC, HDL, smoking status and diabetes (D'Agostino et al., 2008). This Framingham Risk Score (FRS) was developed using cox regression to investigate the 12 year risk of a first CVD event using a sample of 8491 Framingham study participants. The FRS does very well at predicting various CVD events including CHD, Stroke, Intermittent Claudication, and Congestive Heart Failure. The score is useful in clinical settings because it is simple and based on fundamental cardiovascular variables that would be gathered in relatively routine checks. It has been incorporated into many simple online calculators for a quick estimate of 12 year first-time CVD risk. See Appendix A for FRS scoring tables adapted from D'Agostino et al. 2008.

The FRS is not without critique however, with some research groups pointing to its lack of certain factors such as ethnicity, and other risk factors as flaws that can be addressed by a more robust risk prediction model. The SCORE project in Europe developed as a collaboration between 12 large cohort studies, collectively including over 200,000 participants, to devise a risk prediction model for Europeans (Conroy et al., 2003). Like the FRS, SCORE includes age, sex, smoker status, TC, HDL, and SBP, although age is included not as a risk factor in itself but as a measure of exposure time to other risk factors. The model also includes nationality as a risk modifier by identifying certain populations as “high-risk” (Russia, Latvia, Georgia etc.) and others as “low-risk” (Germany, United Kingdom, Italy etc.). SCORE is somewhat unique in comparison to other risk models like Framingham in that it specifically predicts fatal cardiovascular events over a 10 year period, and not cardiovascular events based on a clinical threshold. Unlike several other risk models, SCORE does not include diabetes due to a data limitation in that not all of the included cohort studies had diabetes data (Conroy et al., 2003).

Other models have attempted to include data on risk factors that they felt were lacking in Framingham’s original risk scores. For example, the ASSIGN score from the Scottish Heart Health Extended Cohort includes family history and social deprivation in addition to the traditional FRS risk factors (Woodward, Brindle, & Tunstall-Pedoe, 2007). The PROCAM scoring scheme for coronary event risk incorporates family history and additional serum lipid levels including LDL and TRIG (Assmann, Cullen, & Schulte, 2002). The Reynolds Risk Score for women was developed to specifically address the large number of coronary events that were occurring in women who did not have the

risk factors included in the older Framingham risk models (Buring & Cook, 2007; Khot et al., 2003). In their model, based entirely on coronary event risk in women, they included additional apolipoproteins, C-Reactive Protein (CRP), and parental history, among other factors. In addition to these risk factors, diabetes was conceptualized not dichotomously, but as a continuous variable reflecting hemoglobin A1C levels. While the inclusion of additional risk factors may seem to create a more inclusive model, they complicate the original conception behind cardiovascular risk prediction models in that they should be simple and easily applicable in an office setting. Furthermore, there is some evidence that the simpler models like FRS and SCORE still outperform more complex models like PROCAM in terms of determining absolute CVD risk over the time periods they specify (Versteylen, Joosen, Shaw, Narula, & Hofstra, 2011).

One of the most recent attempts to formulate a CVD risk prediction model that includes Framingham's base risk factors but addresses ethnicity concerns comes from a 2014 report from the American College of Cardiology/American Heart Association (Goff et al., 2014). This risk model specifically predicts the risk of an arteriosclerotic cardiovascular event, including heart attack and stroke, and is abbreviated ASCVD risk (arteriosclerotic cardiovascular disease). In an attempt to address a flaw in the FRS, primarily that it was based on a predominantly white New-England sample, the ASCVD risk score includes a separate risk algorithm for black patients in addition to separate algorithms for men/women and hypertensive treatment/no-treatment. Besides these additions, the score is still derived from age, TC, HDL, SBP, smoker status, and diabetes just like the FRS in an attempt to keep the score based on routinely collected data. Other risk factors including DBP, family history, GFR, and BMI were investigated,

but they did not significantly improve model discrimination for 10-year ASCVD. Unlike the FRS, the ASCVD score has not been adapted to a simple point scoring system but is still based on an easily implemented algorithm and can similarly be quickly provided by various online calculators. See Appendix B for risk scoring algorithms adapted from Goff et al. 2013.

It is evident that there is a growing number of CVD risk prediction models presently in circulation, and this can create a problem for physicians trying to determine which model to use in their own patients. A recent review expanded on this issue, claiming that the number of risk models currently in use is excessive, and more efforts should be made to externally validate existing models using large epidemiological datasets rather than create new prediction models (Damen et al., 2016). Aside from the FRS and SCORE, very few of the models in circulation have undergone rigorous external validation (Damen et al., 2016). Some have suggested that risk prediction models are most appropriately used for individuals who resemble the study sample from which the model was derived (e.g. FRS for white New-England residents; Wilson et al 1998). Regardless of the issues of oversaturation of risk models and demographic concerns, these models are still extremely useful for predicting CVD events in patients who may have multiple marginal risk factors that may not warrant individual treatment (D'Agostino et al., 2008; Grundy et al., 1999; Wilson et al.,1998).

1.6.2. Using Cardiovascular Risk Prediction Models beyond CVD

Section 1.2. established that there is an extensive literature base associating cardiovascular risk factors with cognitive function, and Section 1.5. discussed growing evidence that cardiovascular risk factors may predict MCI risk. It is possible that an

aggregation of cardiovascular risk factors may interact to increase MCI and cognitive decline risk in a similar manner to predicting CVD incidence. Current risk models are based on specific CVD outcome events like CHD, but they may have some use in predicting other conditions like MCI given what is now known about cardiovascular risk factors and their ability to predict other conditions outside coronary events alone, including dementia (Miia Kivipelto, Ngandu, & Fratiglioni, 2005; J. Luchsinger et al., 2005; Whitmer, Sidney, Selby, Claiborne Johnston, & Yaffe, 2005). Despite the models being tailored for another condition, they are still based on fundamental cardiovascular risk factors, and may elucidate the role of these variables in MCI risk. Similar approaches have been used to assess the relationship between cardiovascular risk profiles and cognitive function, with Framingham's stroke risk profile shown to predict not only stroke risk, but cognitive decline in general (Elias et al., 2004). In some cases it has been reported that cardiovascular risk profiles have bested even specifically developed dementia risk scores in the prediction of future cognitive impairment (Kaffashian et al., 2013).

1.7. Objectives and Hypotheses

1.7.1. Primary Objectives

The primary objectives of this study will be to address the current gaps in the cardiovascular risk factor and MCI literature using the large community-based sample of the Maine Syracuse Longitudinal Study (MSLS). Hypotheses are based on previous studies from the MSLS associating cardiovascular risk factors with cognitive impairment, as well as the literature reviewed in Section 1.5. speculating an association between cardiovascular risk factors with MCI and Dementia. All hypotheses are

expected to hold under adjustment for basic model covariates including age, sex, years of education, and ethnicity. Primary objectives are as follows:

1. Determine whether cardiovascular risk factors including SBP, GFR, THCY, Serum Lipids (TC, HDL, LDL, TRIG) and Diabetes predict MCI prospectively. Additionally, determine whether arterial stiffness associates with MCI cross-sectionally.

    Hypothesis: We predict that higher SBP, THCY, and TRIG will be associated with higher MCI risk and that higher MCI risk will be seen is diabetics. We also predict that HDL and GFR will be associated with lower prospective MCI risk. No relationship between TC and LDL with MCI risk is expected. Finally, we predict higher PWV among those categorized as MCI compared to CN.

2. Determine whether APOE genotype moderates the relationship between the cardiovascular risk factors included in this study and MCI.

    Hypothesis: We predict that APOE genotype will moderate the relationships predicted in Objective 1 such that the presence of an APOE ε4 will exacerbate the direct relationship between SBP, THCY, TRIG, and PWV with MCI, and attenuate the inverse relationship between HDL and GFR with MCI.

3. Determine whether an aggregation of cardiovascular risk factors categorized dichotomously into disease/non disease states (hypertension, CKD, diabetes etc.) predicts greater MCI risk prospectively. This aggregation is represented in the MSLS Cardiovascular Risk Factor Scale (MSLS-CVRFS; See Section 2.5.1. in the Methods).

    Hypothesis: We predict that a higher score on the MSLS-CVRFS will prospectively predict greater MCI risk.

4. Determine whether existing cardiovascular risk models designed to predict CVD over a 10-12 year period also predict MCI risk. The two models tested in this study will be the FRS (D'agostino 2008; See Section 2.5.2) and the ASCVD Risk Score (Goff 2013; See Section 2.5.3.)

Hypothesis: We predict that both the FRS and ASCVD Risk score will prospectively predict greater MCI risk.

1.7.2. Secondary Objectives

Secondary objectives of this study involve supplementary analyses related to the findings of the above primary objectives.

1. Compare the three cardiovascular risk scales used in this study (CVRFS, FRS, and ASCVD Risk Score) in their ability to predict MCI.

Hypothesis: While we expect that all three scales will predict higher MCI risk, we predict that the FRS and ASCVD Risk Scores will perform similarly and both outperform the CVRFS. The rationale for this hypothesis is based on the fact that the FRS and ASCVD Risk Score include critical demographic information including age, sex, education whereas the CVRFS is based composed only of cardiovascular variables.

2. Determine whether the CVRFS prospectively predicts cognitive performance measured on a continuum, as opposed to a dichotomous MCI diagnosis. The cognitive composites included in this analysis are outlined in Section 2.3., and are the same measures that determined MSLS MCI diagnosis (See Section 2.6.).

Hypothesis: We expect the CVRFS to prospectively predict each of the cognitive composite scores (Verbal Memory, Visuospatial Organization and Memory,

Scanning and Tracking, Working Memory, Executive Function, and Global Function) in linear regression models including age, sex, education, and ethnicity.

2. METHODS

2.1. The Maine Syracuse Longitudinal Study Design

The Maine Syracuse Longitudinal Study (MSLS) was started in 1974, and has assessed the relationship of cardiovascular health to cognitive functioning over several decades. Initially, the study was primarily interested in idiopathic and uncomplicated hypertension but has since expanded to include various cardiovascular risk factors including arterial stiffness, diabetes, plasma homocysteine, cholesterol levels, kidney function, cardiovascular diseases, and nutritional determinants of cognitive performance, including vitamins. The MSLS includes seven waves of examination with seven cohorts of participants defined by time of entry into the study. A total of 2464 participants have participated in at least one examination (See Table 3.). The first four waves of the study were conducted at SUNY Heath Science Center Upstate New York via collaboration between Merrill F. Elias, Principal Investigator, and David H. P. Streeten, investigator and Professor of Medicine. In 1996 the Maine Syracuse Longitudinal Study acquired its own laboratory space in Syracuse, New York but

Table 3. Design of the MSLS

	W1	W2	W3	W4	W5	W6	W7
C1	E_1 →	E_2 →	E_3 →	E_4 →	E_5 →	E_6 →	E_7
C2		E_1 →	E_2 →	E_3 →	E_4 →	E_5 →	E_6
C3			E_1 →	E_2 →	E_3 →	E_4 →	E_5
C4				E_1 →	E_2 →	E_3 →	E_4
C5					E_1 →	E_2 →	E_3
C6						E_1 →	E_2
C7							E_1
N	234	494	679	717	1506	1176	841

W= Wave C=Cohort E=Exam

continued to collaborate with medical staff at SUNY Health Sciences Center. Figure 4. displays the different locations involved in the MSLS study including where specific assays were done.

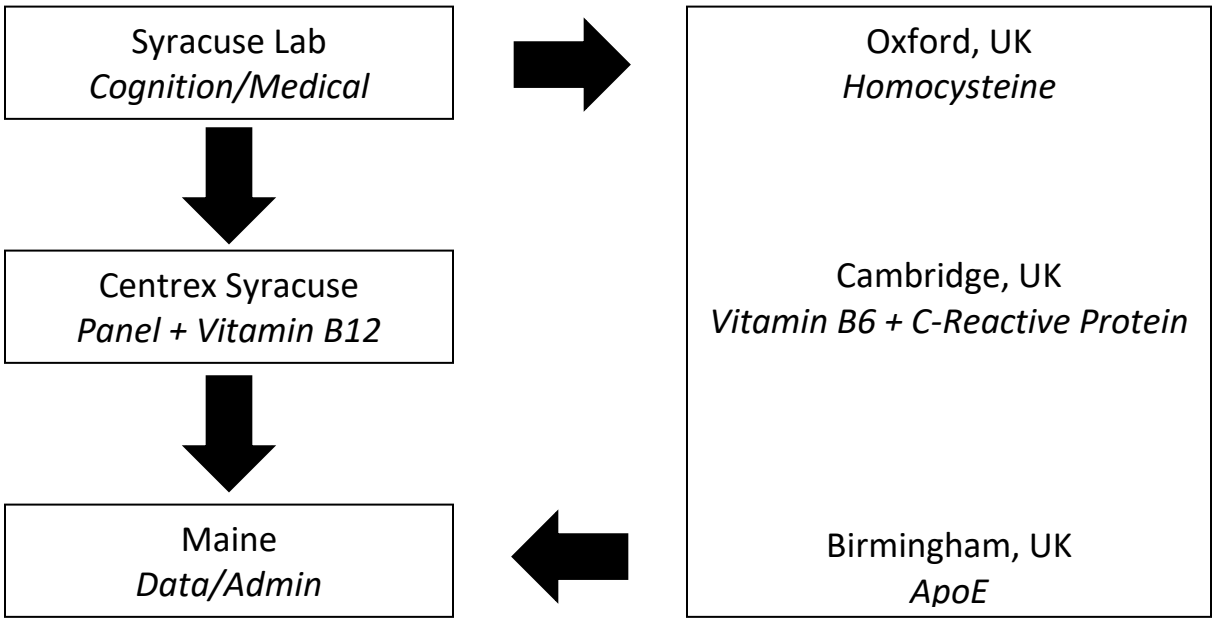

Figure 4. MSLS Structure and Assessment Locations

The MSLS has a long history of relating cardiovascular risk factors to cognitive functioning along a continuum, setting the framework for using similar risk factors to predict a dichotomous variable like MCI. A recent review of the literature summarizes these studies in the context of the history of the study of cognitive performance and hypertension (M.F. Elias et al., 2012). The MSLS was the first longitudinal study designed to examine relations between hypertension and cognition over the lifespan, following a small initial study by Wilkie and Eisdorfer (Wilkie & Eisdorfer, 1971). Here we summarize data from particularly illustrative studies.

The MSLS has previously shown a negative relationship between high blood pressure and cognitive function (Crichton, Elias, Davey, & Alkerwi, 2014; M F Elias,

Robbins, Elias, & Streeten, 1998; P. K. Elias, Elias, Robbins, & Budge, 2004), as well as blood pressure variability across measurements and cognitive function (Crichton, Elias, Dore, Torres, & Robbins, 2014). The study has furthermore evidenced relationships between lipid profiles and cognitive function (Crichton, Elias, Davey, Sullivan, & Robbins, 2014), arterial stiffness as measured by PWV and cognitive function (M.F. Elias et al., 2009; M F Elias, Crichton, & Abhayaratna, 2015), as well as an interactive effect of the APOE ε4 allele and diabetes on cognitive functioning (G. A. Dore et al., 2009). An interaction between APOE genotype and homocysteine has also been reported (M F Elias et al., 2008). Many of these studies are prospective in design, using risk factors to predict cognitive function after a period of several years. The current study uses a similar methodology to these past projects, which support our preliminary hypotheses in their findings.

2.2. Procedure

Paper and pencil questionnaires including general medical information, demographic data, job stress questions, sleep disturbance, Cornell Medical Index, and health habits (vitamins, supplements, smoking, alcohol consumption etc.) are completed at home. Participants then came into the lab around 9 AM following a fasting period from midnight (unless diabetic). Participants in the study provided medical interview information on physical health, mental health, and demographics prior to neuropsychological testing. Blood samples were taken first when the participant arrived, followed by fifteen blood pressure measurements (five each recumbent, sitting, and standing) and pulse wave analysis (PWV). Following a light breakfast, a physical examination with medical history review and review of current treatments and

medications was done. The participant then participated in the MSLS Neuropsychological Battery consisting of over twenty tests and subscales including the Wechsler Memory Scale-Revised (WMS-R), the Wechsler Adult Intelligence Scale-III (WAIS-III), Mini Mental State Exam (MMSE), and Boston Naming Test among several other assessments. Assessment order was identical across all participants. Cognitive testing was done at each of the seven waves of the studies with small variations in test types due to scale revisions, and measurement of additional cognitive domains. Following the examination a summary of each subject's medical and cognitive examination was sent to them with a request that they (the study participants) contact their family physician or other specialist and go over the report with them.

2.3. The MSLS Cognitive Test Battery

Cognitive performance was first assessed via the original Wechsler Intelligence Scale and the Halstead-Reitan Neuropsychological Test Battery. In 1993 the Framingham Test Battery was added as a special subset of tests. Eventually specific tests were chosen to be given at each wave and defined as the Maine Syracuse Longitudinal Test Battery. The test battery used continuously distributed cognitive tests, however many clinical tests were available for use in diagnosis of clinical impairment.

The "MSLS Battery" (core battery) tests used to derive composite scores (factors or domains) and the names of the composite scores are outlined in Appendix C. The scores used were all continuously distributed and were largely taken from the Wechsler Intelligence Scale and the Wechsler Memory Scales. These composite scores include Visual Spatial Memory and Organization, Verbal Memory, Working Memory, Scanning and Tracking (See Appendix C for a list of composite scores and tests factored into

each composite). WAIS Similarities loaded about equally across factors and thus was used as an independent single test of abstract reasoning. Later an executive functioning composite was added including Trail Making and Controlled Oral Word Associations. These composite scores are represented in Z scores with a mean of 0 and SD of 1, reflecting performance relative to the entire community-based sample. The core battery also included administration of the MMSE, which is sensitive to cognitive decline over repeated assessments.

2.4. Cardiovascular Risk Factors

2.4.1. Blood Pressure

Blood pressure (mmHg) was measured in the MSLS using a pressure cuff with a Critikon Dinamap ProCare 100. Five measures each were taken in standing, sitting, and reclining position, with a five minute interval in between each measurement. For these analyses, an average of all 15 measurements was used for systolic blood pressure (SBP). The average BP across all 15 measurements was also used as a cut off score for hypertension. Pulse Pressure (PP) was calculated by taking the difference in average SBP and DBP (see Crichton et al. 2014).

2.4.2. Arterial Stiffness

As part of a new grant and a new direction at Wave 7 of the MSLS, arterial stiffness was assessed non-invasively using PWV analysis. Using the SphygmoCor system (AtCor Medical), PWV was measured in supine position with applanation tonometry. Carotid-femoral path length was defined as the difference between the surface distances of the suprasternal notch, the umbilicus, and the femoral pulse, as well as the suprasternal notch and the carotid pulse. Transit time was estimated in 8 to

10 sequential Electrocardiogram-gated femoral and carotid waveforms as the average difference between the start of the femoral and carotid waves. PWV was calculated as the carotid-femoral path length (meters) divided by the carotid-femoral transit time (seconds).

2.4.3. Homocysteine

Plasma Hcy levels were measured using a fluorescence polarization immunoassay on an Abbot IMx auto-analyzer at the University of Oxford. Blood samples were drawn following a period of fasting from midnight. The coefficient of variation for the tHcy assays was less than 3.5% (M F Elias et al., 2006).

2.4.4. Serum Lipids

Serum lipids including TC, HDL, LDL, and TRIG were obtained from fasting blood samples using standard assay methods at Centrex Clinical Laboratories. Lipid levels are presented in milligrams per deciliter blood. Details of blood draws and assays can be seen in Elias et al. (2006).

2.4.5. Diabetes

Type 2 Diabetes in the MSLS was defined objectively by treatment with insulin or glucose lowering medications, or by a fasting glucose greater than 126 mg/dL determined by serum analysis by Centrex Clinical Laboratories.

2.4.6. Renal Function

Kidney function in the MSLS is measured by GFR using the CKD-EPI formula comprising age, sex, ethnicity, and serum creatinine. Fasting blood samples were collected in serum separator tubes and sent to Centrex Clinical Laboratories in Syracuse, NY for determination of serum creatinine. Serum creatinine was determined

using a two-point rare test type on a Johnson and Johnson Vitros Intrument. Coefficient of variation was less than 5%.

2.4.7. APOE

APOE genotyping was in the laboratory of David A. Smith, Chairman of the Department of Pharmacology, University of Oxford, UK, using state of the art methods of polymerase chain reaction and restriction enzyme digest with HhaI (Hixson & Vernier, 1990). Genotyping was done with interest in determining the presence of the E4 allele, a risk factor for several brain pathologies and cognitive impairment in late life.

2.5. Cardiovascular Risk Scores

2.5.1. The MSLS Cardiovascular Risk Factor Scale

The MSLS Cardiovascular Risk Factor Scale (MSLS-CVRFS) is a count of dichotomized cardiovascular conditions and biometrics intended to represent a participant's cardiovascular health in terms of clinically defined risk factors. Unlike the other risk scores presented in this study, the scale is not intended to predict risk for future CVD but is rather intended to represent a current assessment of a participant's cardiovascular condition. The current version of the scale represents 12 risk factors that either reflect binary disease states (hypertension, diabetes etc.) or have been dichotomized based on clinically recommended cutoffs (lipid levels, kidney function etc.). The risk factors included in the scale are as follows: hypertension (≥140 SBP and/or ≥90 DBP), diabetes, cardiovascular disease (history of 1 or more of angina pectoris, coronary artery disease, myocardial infarction, heart failure, and transient ischemic attack), Obesity (≥30 BMI), Apoe ε4 (presence of 1 or 2 ε4 alleles), smoking (current smoker), Low HDL (<40 mg/dL), High LDL (>160 mg/dL), High TRIG (>200

mg/dL), High THCY (>13 μmol/L), High CRP (>3 mg/L), Low EPI GFR (<60 mL/min). These risk factors were then aggregated to form the CVRFS, which ranges in score from 0 (no risk factors) to 12 (all 12 risk factors included in the scale).

Five hundred and ninety participants in the sample had complete data for all 12 cardiovascular risk factors (35 participants were excluded for missing data) and a CVRFS score was calculated for each. Figure 5. displays the frequency of each score on the cardiovascular scale (e.g. 56 individuals in the sample had no cardiovascular risk factors). The mean CVRFS score was 2.67 (SD=1.75) with a median and mode of 3.

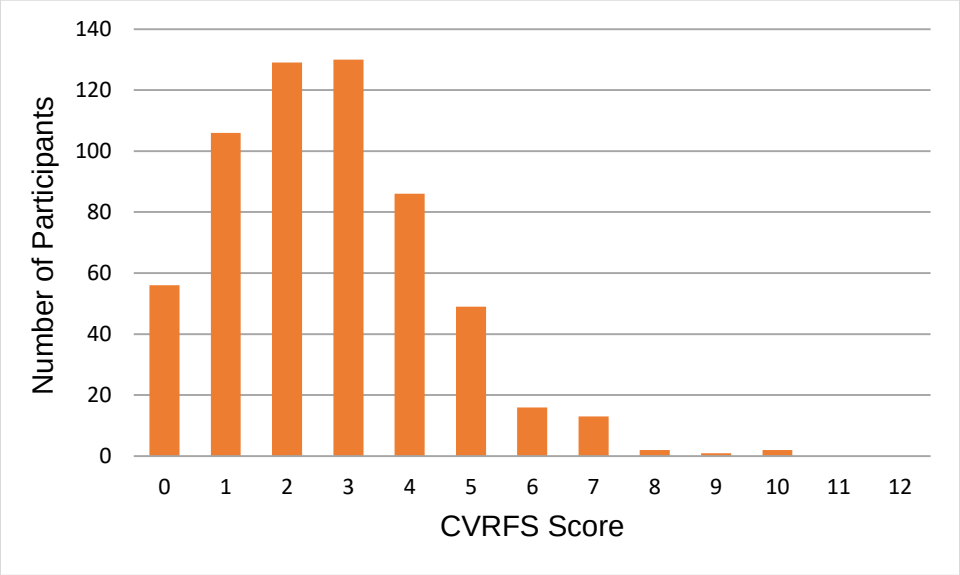

Figure 5. Frequency of CVRFS Score in Study

The CVRFS is slightly skewed due to a small number of individuals (n=5) having scores beyond CVRFS=7 (see Figure 5.). To adjust the scale and meet assumptions for normality required for a linear regression, the scale was truncated to include these five individuals in a new CVRFS=7+ category (see Figure 6.). This new distribution is relatively normal and was used to conduct the linear regressions. With truncation the CVRFS had a mean of 2.65 (SD=1.70), a median of 3, and a mode of 3. Although normality is not a requirement for logistic regression the truncated version of the CVRFS was used in all analyses for consistency.

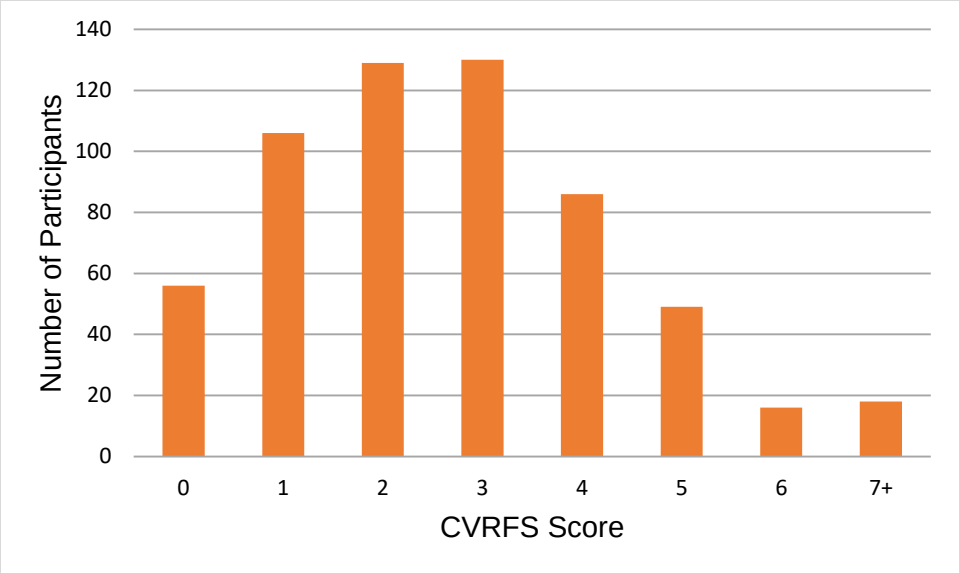

Figure 6. Frequency of Truncated CVRFS Score

Table 4. displays the frequency of each risk factor at various levels of the CVRFS. Hypertension was the most common risk factor at each level of the scale, representing 32% of the participants who had just one risk factor, and was present in 95% of the participants who scored ≥ 5 on the CVRFS. Proportion of each risk factor increased with increasing CVRFS score, and while certain risk factors were more common (hypertension, obesity etc.) we feel each risk factor included in the scale is

adequately represented. Basic demographic info is also displayed. On average, the groups that scored higher on the CVRFS appeared to be slightly older, less educated, and had a higher proportion of males and non-white individuals.

Table 4. Proportion of Sample with each Risk Factor in the CVRFS by Number of Risk Factors + Demographics

Risk Factor	CVRF=0 N= 56	CVRF=1 N=106	CVRF=2 N=129	CVRF=3 N=130	CVRF=4 N= 86	CVRF=5+ N=83
Hypertension	0	.32	.56	.74	.81	.95
Diabetes	0	.01	.03	.09	.16	.43
Cardiovascular Disease	0	0.00	.05	.15	.17	.39
Obesity	0	.05	.33	.58	.63	.76
Apoe ε4	0	.24	.25	.30	.41	.41
Current Smoker	0	.03	.07	.08	.12	.22
Low HDL	0	.01	.05	.12	.22	.48
High TRIG	0	.02	.04	.10	.24	.51
High LDL	0	.10	.12	.15	.21	.14
High THCY	0	.02	.05	.09	.13	.33
High CRP	0	.17	.35	.50	.67	.72
Low GFR	0	.04	.10	.10	.22	.41
Demographics						
Age (years)	58.93 (11.3)	61.34 (13.15)	63.07 (13.09)	61.48 (10.65)	64.78 (10.72)	62.71 (11.12)
Sex (% female)	71%	66%	60%	62%	58%	49%
Education (years)	15.8 (2.34)	14.95 (2.82)	14.50 (2.883)	14.93 (2.57)	14.41 (2.42)	13.33 (2.61)
Ethnicity (% white)	100%	94%	96%	95%	93%	80%

Standard deviation presented in parentheses where applicable

2.5.2. The Framingham Risk Score

The FRS is described in detail in Section 1.6.1. The score was calculated at baseline for MSLS participants consistent with the scoring tables presented in D'Agostino et al 2008 and Appendix A. The FRS is based off an individual's sex, age, HDL, TC, SBP, hypertensive treatment, smoker status, and diabetic status. A higher FRS score indicates a higher CVD risk over 12 years follow-up. The FRS was only

utilized in this study for participants with complete data for the variables included in the algorithm (n=615). The sample had a mean FRS of 12.87 (SD=5.54) with risk scores ranging from -3 to 25. The FRS can also be converted to a risk percentage for CVD using conversion tables presented in D'Agostino et al 2008, though this approach was not used for this study.

2.5.3. The Arteriosclerotic Cardiovascular Disease Risk Score

The ASCVD Score is described in detail in section 1.6.1. The score is represented as a 10-year risk percentage for arteriosclerotic CVD. The ASCVD risk score was calculated for MSLS participants consistent with the risk algorithms presented in (Goff et al., 2014) and Appendix B. Like the FRS, the ASCVD includes sex, age, HDL, TC, SBP, hypertensive treatment, smoker status, and diabetic status. The scoring algorithm also incorporates ethnicity, with separate coefficients for whites and African Americans. ASCVD risk score was only calculated for white or African American participants who had complete data for the variables included in the algorithm (n=607). The sample had a mean ASCVD risk percentage of 15.29% (SD=16.32%) and scores ranged from 0% to 85%.

2.6. Defining MCI in the MSLS

The proposed study uses data from the final two waves of the MSLS (wave 6 and 7) for two reasons: 1). These waves offer the most complete and comprehensive set of data in terms of cardiovascular and cognitive variables; and 2). these waves have the highest average age in the study (Wave 6 M=62.43, SD=12.85; Wave 7 M=65.28, SD=12.72).This age range targets the potential at-risk population for MCI. Given the importance of previous functioning to the diagnosis of MCI, it is necessary to assess

decline in function over time (from Wave 6 to 7). 762 study participants were assessed at both examinations. Of these participants, 625 had complete cognitive battery data for both waves. These examinations were an average of 5 years apart (M=4.64, SD=.72), allowing a decline in function from a previous baseline. Therefore, MCI diagnosis is made at Wave 7 if the criterion for decline is met.

The MSLS has not included a formal diagnosis of possible MCI prior to the proposed work, albeit dementia has been defined. The MSLS categorization for possible MCI is based on common MCI criteria outlined in Section 1.4.2. The individual must be free from dementia, have maintained independence in daily function, and show a decline in cognitive function from previous level. Thus for both waves 6 and 7, exclusions from the sample were for dementia (as defined by the MSLS dementia committee and current criteria). Subjects with diagnosed alcoholism and psychotic mental illness or institutionalization, or who could not speak English were excluded from the study the study at its inception. There was no restriction on age at entry into the study. However, it has always been the policy that individual investigators may use their own set of exclusions as dictated by study goals. Such is the case for the proposed work.

The criteria used for diagnosis of MCI are sensitive to single-domain or multi-domain MCI in that the individual would be marked as possible MCI with a large decrease in performance in one domain, or with smaller decreases in performance across multiple domains. Initially, we used the commonly employed criterion of a drop in performance of 1 SD, and considered this a sign of possible MCI. A drop of .5 SD in multiple domains (or Global Function) was considered possible MCI to include multi-

domain phenotypes in order to identify persons who show a drop in performance in multiple cognitive domains. These domains are outlined in Appendix C. However, because archival diagnosis of MCI can be difficult, we decided to increase the requirements for possible diagnosis to a 1.5 SD drop in a single domain or multiple 1 SD drops across several domains (or Global Function). These stricter criteria were used in an effort to limit false positive diagnoses. Additionally, a drop in MMSE score of 4 or more was considered an additional marker of possible MCI, as this is a large drop over 5 years. This criterion alone does not suffice as an indicator of MCI because persons can drop 3 points or more and return to normal functioning on the MMSE at a third measurement point. Figures 7-9. display the pattern of cognitive changes from baseline to follow-up between participants categorized as MCI vs CN (Non-MCI).

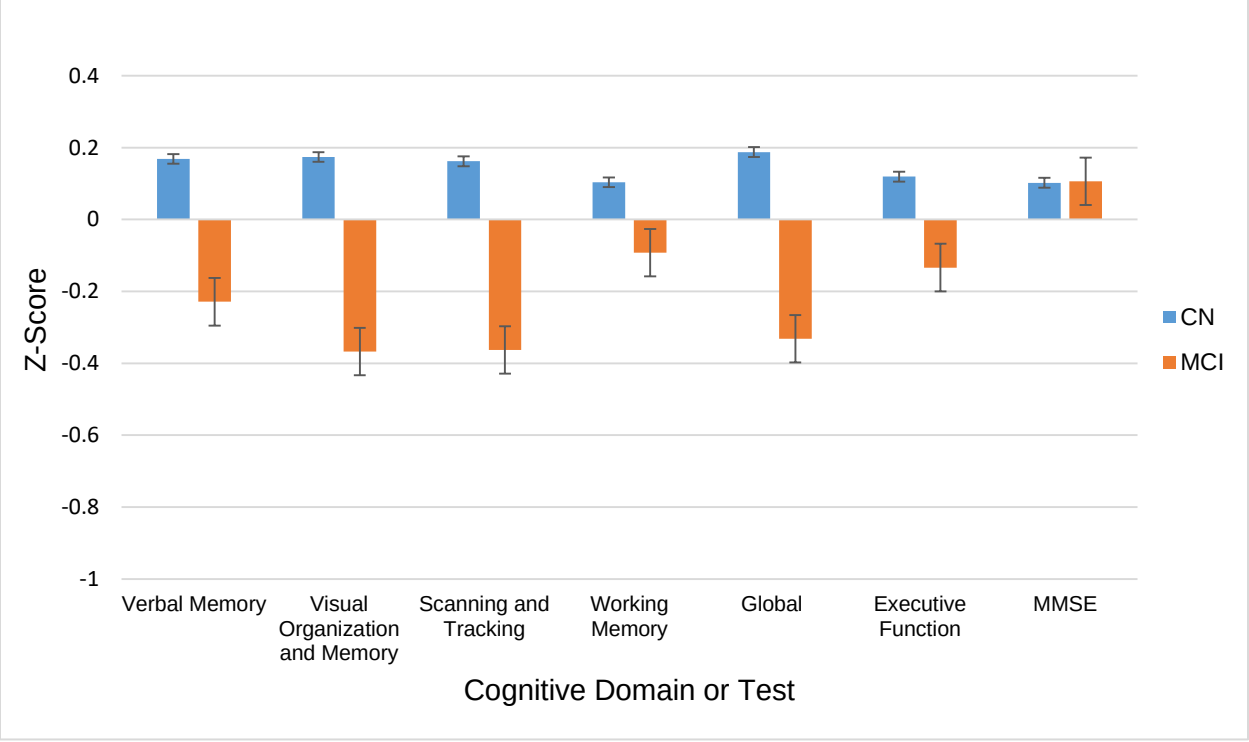

Figure 7. Baseline Cognitive Composite + MMSE Standardized Scores

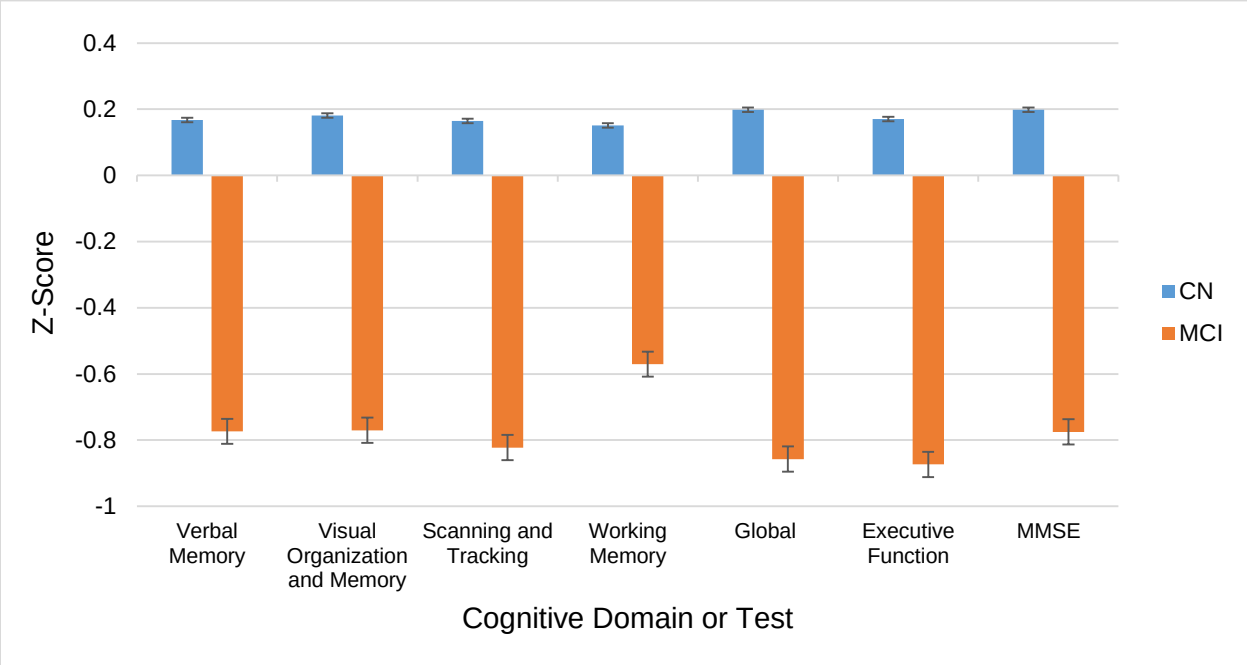

Figure 8. Follow-Up Cognitive Composite + MMSE Standardized Scores

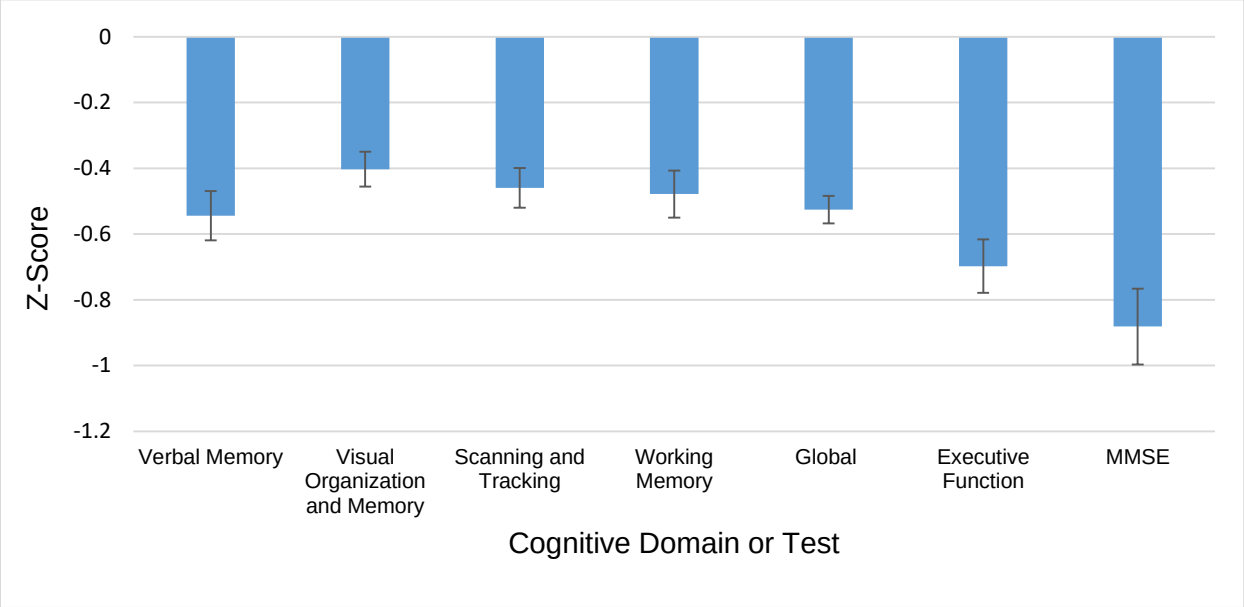

Figure 9. Average drop in performance on Cognitive Composites and MMSE for MCI Sample

2.7. Sample Characteristics

Following exclusions for probable dementia (n=6), a total sample of 625 individuals was examined at both Waves 6 and 7 of the MSLS and had complete cognitive battery data to inform MCI diagnosis. 96 (15.4%) participants met the criteria for probable MCI outlined in Section 2.6. This proportion is consistent with other large community based studies and MCI prevalence meta-analyses (Ganguli et al., 2010; R. Petersen et al., 2010). Subsequently, 529 participants were considered free from dementia or MCI and were categorized as Non-MCI or CN. Average baseline age for the non-MCI sample was 60.70 (SD=11.50), whereas average age for the MCI sample was 69.01 (SD=11.51). Activities of daily living were not compromised in either sample, consistent with common MCI diagnostic criteria. The sample was largely community dwelling individuals who should be representative of the normal population for these age ranges. A preliminary look at the demographic data suggests some difference in cardiovascular risk factors between the two groups, with the MCI sample showing slightly higher BP, PWV, THCY, and higher incidence of diabetes and stroke (See Table 5. on the following page).

Table 5. Demographics Table

Variable	Baseline (Wave 6)		Follow-up (Wave 7)	
	Non-MCI (n=529)	MCI (n=96)	Non-MCI (n=529)	MCI (n=96)
Age (years)	60.70 (11.50)	69.01 (11.51)	65.39 (11.46)	73.61 (11.55)
Sex (% Female)	63%	49%	63%	49%
Education (years)	14.63 (2.70)	14.49 (2.87)	14.70 (2.72)	14.36 (2.86)
Ethnicity (% white)	92%	96%	92%	96%
MMSE (Total Score)	28.33 (1.87)	28.34 (1.91)	28.09 (1.95)	25.80 (2.86)
Global Composite (Z-Score)	.19 (.90)	-.33 (.93)	.20 (.92)	-.86 (1.00)
Diabetes (% Diabetic)	10%	18%	15%	22%
CVD (% Have/had CVD)	11%	20%	16%	31%
BMI	29.63 (6.19)	28.90 (4.69)	29.98 (6.88)	28.28 (4.84)
SBP (mmHg)	129.52 (21.47)	134.91 (23.07)	129.89 (19.91)	136.00 (23.16)
PWV (m/s)	n/a	n/a	10.47 (2.95)	11.78 (3.61)
THCY (µmol/L)	9.56 (3.23)	10.42 (3.09)	10.40 (3.69)	11.74 (3.97)
TC (mg/dL)	203.75 (40.12)	196.25 (39.69)	188.56 (39.42)	174.15 (40.51)
HDL (mg/dL)	54.79 (15.87)	51.01 (13.84)	53.02 (49.25)	49.25 (13.82)
LDL (mg/dL)	121.98 (33.65)	116.54 (34.36)	112.59 (32.41)	101.04 (34.96)
TRIG (mg/dL)	139.47 (109.04)	147.47 (100.59)	116.64 (77.96)	118.82 (59.91)
GFR (mL/min	79.02 (16.24)	69.46 (17.96)	66.31 (15.74)	58.21 (16.23)
APOE (% have at least 1 ε4)	28%	30%	28%	30%
Smoking (% current smoker)	11%	3%	n/a	n/a
Hypertensive Meds (% Treated)	47%	57%	57%	70%
CVRFS	2.57 (1.69)	3.09 (1.68)	n/a	n/a
FRS	12.44 (5.57)	15.24 (4.75)	n/a	n/a
ASCVD Risk Score (%)	13.35% (14.35%)	25.75% (21.59%)	n/a	n/a

2.8. Statistical Analysis Strategy

2.8.1. Logistic Regression

Given the nature of our continuous predictor variables (cardiovascular risk factors such as BP, PWV, and tHcy) and a dichotomous outcome variable (MCI; yes/no), we will be employing a logistic regression model (Hosmer & Lemeshow, 1989). Unlike traditional linear regression, which has been often been used in previous MSLS studies to assess the relationship between continuous predictor variables and cognitive

performance along a similar continuous scale, logistic regression provides probabilities of a binary outcome dependent on the predictor variables included in the model. These odds ratios fit the medical model of binary diagnosis and can be used to predict MCI risk based on the levels of several cardiovascular variables and covariates. Assumptions are largely in common with linear regression with regards to absence of multicollinearity or outliers with undue leverage on the regression equation. However, logistic regression does not require normally distributed predictor variables (Hosmer & Lemeshow, 1989). Because change in probability is not linear, the logistic regression maps observed data onto a logistic function containing the natural logs of each possible odds ratio. This logit scale is continuous, therefore the log of the odds ratios form a linear function of the predictor variables. This procedure is useful for assessing relative risk given a model of cardiovascular variables and covariates, and will indicate whether an aggregation of one or more risk factors increases the likelihood and individual will be in the MCI group. One important assumption in logistic regression analysis is that associations between risk and outcome variables are linear, albeit in the absence of linearity one employs other scaling methods, e.g. examine quartiles of performance rather than scaling predictors as continuously distributed. In this study logistic regression will be used to assess the association of various cardiovascular risk factors and MCI risk. It will not be used as a classification procedure.

2.8.2. Covariates

Like traditional linear regression, logistic regression also allows for the inclusion of covariates in the model in a way similar to linear regression analysis except that the outcome is a yes/no dichotomy. Our selection of covariates is based first on theory and

clinical relevance, and secondly on empirical examination of relations between predictors and outcomes. In classical epidemiology there is a requirement that a variable not be considered a confounder unless it relates to the predictor and outcome. However, consistent with the behavioral and social sciences we consider theory and clinical relevance as of the first importance in adding variables.

A significant problem in modeling is that too many covariates will reduce total variance to the point where there are no results. Consequently, we model in hierarchical fashion, beginning with zero-order relations, adding a basic demographic mode (age, sex, education, and ethnicity) and subsequent models until model R^2 values indicate no better prediction of outcomes with added models. We also use backward elimination procedures, but always lock theoretically relevant variables in the models. Covariate models in this study will focus on basic demographic info including age, sex, education, and ethnicity.

3. RESULTS

3.1. Cardiovascular Risk Factors Predicting MCI

We prospectively predicted MCI with several cardiovascular risk factors and hypothesized that higher levels of these factors would predict an increased risk of MCI (with the exception of HDL and GFR, which we expected to be associated with lower risk). Table 6. displays the results of a series of logistic regression analyses testing these hypotheses with a zero-order model and a basic covariate model adjusting for age, sex, education, and ethnicity. The assumptions of logistic regression, including Hosmer and Lemeshow tests of model fit, were all met unless otherwise mentioned.

Systolic Blood Pressure (SBP; *b*=.011, p=.026, OR=1.011) and Plasma Homocysteine (THCY; *b*=.069, p=.022, OR=1.071) were both positively associated with MCI as predicted. However neither of these associations remained with adjustment for the basic model covariates (SBP: *b*=-.002, p=.748, OR=.998; THCY: *b*=.018, p=.59, OR=1.019).

High density lipoprotein (HDL; *b*=.-.017, p=.03, OR=.983) and Estimated Glomerular Filtration Rate (GFR; *b*=-.024, p<.001, OR=.976) were both negatively associated with MCI consistent with our initial hypotheses. These associations remained with adjustment for basic model covariates (HDL: *b*=-.02, p=.022, OR=.980; GFR: *b*=-.017, p=.015, OR=.983).

In a cross sectional analysis PWV was significantly associated with MCI (*b*=.122, p=.001, OR=1.130). However this association did not remain under adjustment for the basic model (*b*=.012, p=.806, OR=1.012).

Table 6. Logistic Regression Results: Cardiovascular Risk Factors Predicting MCI with Adjustment for Basic Model Covariates

	Zero-Order					Basic Model Adjustment				
	b	χ^2(df)	p	OR	95% CI (OR)	b	χ^2(df)	p	OR	95% CI (OR)
SBP	0.011	4.927 (1)	0.026*	1.011	1.001:1.021	-0.002	.103 (1)	0.748	0.998	.987:1.01
TC	-0.005	2.828 (1)	0.093	0.995	.990:1.001	-0.003	1.076 (1)	0.3	0.997	.991:1.003
HDL	-0.017	4.689 (1)	0.03*	0.983	.968:.998	-0.02	5.278 (1)	0.022*	0.98	.963:.997
LDL	-0.005	2.053 (1)	0.152	0.995	.988:1.002	-0.003	.848 (1)	0.357	0.997	.989:1.004
TRIG	0.001	0.444 (1)	0.505	1.001	.999:1.002	0.001	2.077 (1)	0.15	1.001	.999:1.003
GFR	-0.024	12.513 (1)	<.001*	0.976	.964:.989	-0.017	5.875 (1)	0.015*	0.983	.969:.997
THCY	0.069	5.277 (1)	0.022*	1.071	1.010:1.136	0.018	.290 (1)	0.59	1.019	.952:1.089
DIABETES	0.618	4.157 (1)	0.041*	1.855	1.024:3.358	0.62	3.622 (1)	0.057	1.859	.982:3.520
PWV^	0.122	10.348 (1)	0.001*	1.13	1.049:1.217	0.012	.06 (1)	0.806	1.012	.923:1.109

* p<.05 ^ cross-sectional analysis

3.2. APOE Interaction Terms Predicting MCI

Theoretically relevant cardiovascular risk factors included in the above analyses and the CVRFS were used to create interaction terms with APOE genotype (ε4 carrier or not). Out of 614 subjects in the present study with APOE data, 442 have no ε4 alleles while 172 are ε4 carriers. There was no main effect of APOE in any of the analyses performed, and in a separate analysis APOE was not significantly associated with MCI in a simple single factor ANOVA [$F(1,612)=.271$, p=.603, η2=.000], with 15.2% of non-ε4 carriers having MCI compared to 16.9% of ε4 carriers having MCI.

Table 7. displays the results of these APOE interaction analyses as part of a logistic regression analysis with a model including both variables in the interaction term, as well as basic model covariates. Of the variables tested, only LDL demonstrated significant interactions with APOE, however Hosmer and Lemeshow model fit statistics suggested the LDL X APOE interaction model did not fit the observed data and should not be interpreted as a significant effect.

Table 7. Logistic Regression Results: APOE Interaction Terms Predicting MCI with Adjustment for Basic Model Covariates

	Zero-Order					Basic Model Adjustment				
	b	χ^2(df)	p	OR	95% CI (OR)	b	χ^2(df)	p	OR	95% CI (OR)
APOE*SBP	0.006	.348 (1)	0.555	1.006	.986:1.028	-0.001	0.005 (1)	0.943	0.999	.976:1.022
APOE*TC	0.003	.308 (1)	0.579	1.003	.991:1.016	0.003	.165 (1)	0.685	1.003	.990:1.016
APOE*HDL	-0.014	0.634 (1)	0.426	0.986	.953:1.020	-0.01	0.319 (1)	0.572	0.99	.957:1.025
APOE*LDL	0.015	3.966 (1)	0.046*	1.015	1.00:1.031	0.014	3.188 (1)	0.074	1.014	.999:1.030
APOE*TRIG	-0.004	2.962 (1)	0.085	0.996	.991:1.001	-0.005	3.553 (1)	0.059	0.995	.989:1.000
APOE*GFR	0.017	1.510 (1)	0.219	1.017	.99:1.046	0.021	2.032 (1)	0.154	1.021	.992:1.051
APOE*THCY	-0.003	.002 (1)	0.962	0.997	.867:1.145	-0.017	0.041 (1)	0.839	0.983	.837:1.155
APOE*DIABETES	0.104	.026 (1)	0.871	1.11	.314:3.923	0.39	.327 (1)	0.567	1.477	.388:5.621

* p<.05

3.3. MSLS-CVRFS and MCI

3.3.1. Analysis

A logistic regression analysis was done to predict possible MCI at 5 year follow up from number of risk factors on the MSLS-CVRFS. Five-hundred and ninety subjects were included in the analysis, with 94 (15.9%) having possible MCI. The sample had a mean CVRFS score of 2.65 (SD=1.70) and a range of 0-7. Refer to Section 2.5.1. in the methods for the full distribution of scores.

3.3.2. Model Fit

A Hosmer and Lemeshow test for model fit determined that the MCI values predicted by the model did not significantly differ from observed values (χ^2=7.441, df=8, p=.49). Therefore the predicted rates by the model reliably matched the observed rates of MCI in the sample, and further interpretation of regression analysis was possible. Figure 10. displays zero-order model predicted MCI relative to observed MCI rates in the sample.

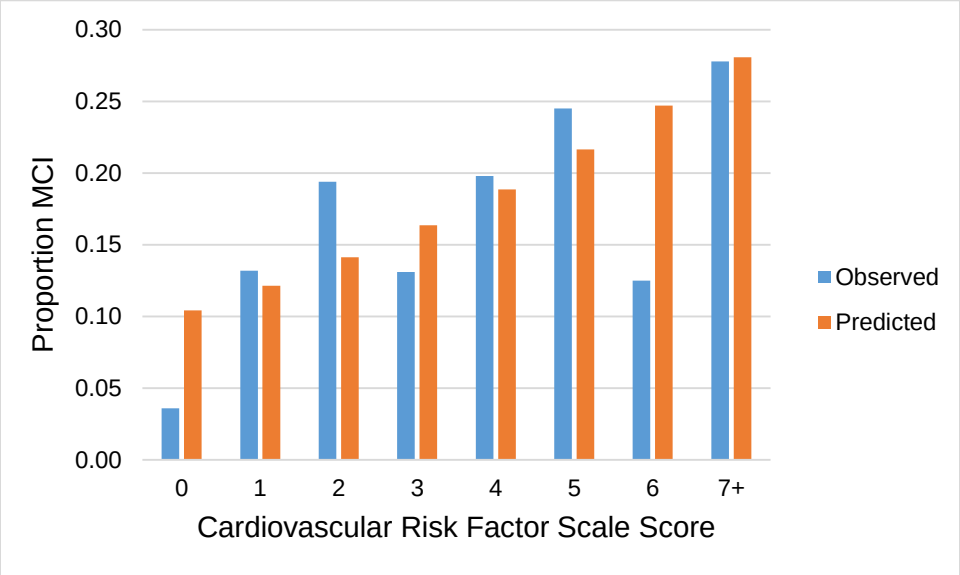

Figure 10. Observed and Predicted MCI Proportion based on CVRFS

3.3.3. Relation of MSLS-CVRFS to MCI

The MSLS-CVRFS score at Wave 6 predicted follow up MCI at Wave 7 with adjustment for the basic model covariates (*b*=.170, $\chi^2(1)=5.469$, p=.019, OR=1.186, 95% CI OR: 1.028-1.368). The MSLS-CVRFS also predicted MCI in a zero-order model (*b*=.173, $\chi^2(1)=7.147$, p=.008, OR=1.189, 95% CI OR: 1.047-1.349). The odds ratio for the full model can be interpreted such that for every 1 unit increase in risk (CVRFS score) the odds associated with MCI increased by 18.6%. However, examination of the data determined that there are not equal units of risk with increases in the MSLS-CVRFS, and therefore a different analysis and interpretation was necessary. As is commonly done we compared different levels of the MSLS-CVRFS to a CVRFS=0 referent group representing zero risk. Table 8. displays odds ratios evidencing increased MCI risk for subjects with an increasing risk factor score as compared to a zero risk factor referent group. However, the apparent reduction in risk moving from

CVRFS=2 to CVRFS=3 warranted further exploration to observe the pattern of increased risk with increased CVRFS score. Table 9. displays the same analysis with different groupings, with CVRFS=2 and CVRFS=3 being grouped together and CVRFS=4+ replacing CVRFS=5+. This reconfiguration of risk factor groups reveals that moving from 1 to 2 or 3 risk factors increased the risk of MCI, but the largest increase in risk was observed in individuals who exceeded 4 on the CVRFS. These comparisons to a CVRFS=0 referent group were made with and without control for the basic covariate model. An additional control for physical activity (metabolic equivalents per week) was made in a separate analysis but the relation between CVRFS and MCI remained significant (p<.05 comparing groups CVRFS=2 or 3 and CVRFS=4+ to referent group).

Table 8. Odds Ratios (Zero-order and Basic Model Adjusted) for Each Level of CVRFS Compared to CVRFS = 0 Referent Group

		Zero-Order			Basic Model Covariates		
CVRFS	N	Odds Ratio	95 % CI	p	Odds Ratio	95 % CI	p
0 (referent)	56	n/a	n/a	n/a	n/a	n/a	n/a
1	106	4.109	0.899 – 18.772	0.068	3.268	.681 - 15.687	0.139
2	129	6.49	1.481 – 28.4363	0.013*	5.227	1.152 - 23.724	0.032*
3	130	4.062	0.906 – 18.216	0.067	3.363	.733 - 15.440	0.119
4	86	6.652	1.4727 – 30.048	0.014*	4.586	.958 - 21.945	0.057
5+	83	7.172	1.586 – 32.442	0.011*	5.638	1.152 - 27.605	0.033*

* p<.05

Table 9. Odds Ratios (Zero-order and Basic Model Adjusted) for Each Level of CVRFS Compared to CVRFS = 0 Referent Group (New Grouping)

		Zero-Order			Basic Model Covariates		
CVRFS	N	Odds Ratio	95 % CI	p	Odds Ratio	95 % CI	p
0 (referent)	56	n/a	n/a	n/a	n/a	n/a	n/a
1	106	4.109	0.899 – 18.772	0.068	3.268	.681 - 15.687	0.139
2,3	259	5.226	1.226 – 22.268	0.025*	4.384	1.007 - 19.083	0.049*
4+	169	7.308	1.700 – 31.425	0.008*	5.067	1.128 - 22.767	0.034*

* p<.05

3.4. FRS and MCI

3.4.1. Analysis

A logistic regression analysis was done to predict possible MCI at 5 year follow up from the FRS. Six hundred and fifteen participants were included in the analysis, with 96 (15.6%) having possible MCI. The sample had a mean FRS of 12.87 (SD=5.54) and ranged from -3 to 25. Figure 11. displays the frequency of FRS in the sample. Because the FRS algorithm includes age and sex, the basic model covariates included in the model for this analysis were limited to years of education and ethnicity.

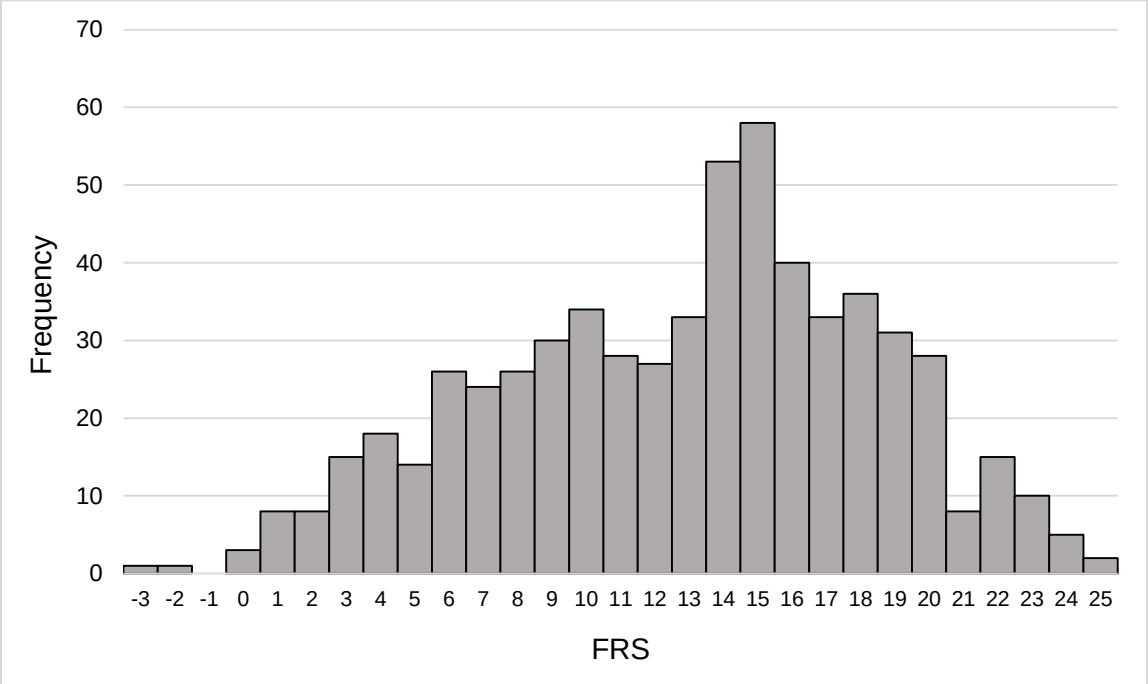

Figure 11. Frequency of FRS

3.4.2. Model Fit

A Hosmer and Lemeshow test for model fit determined that the MCI values predicted by the model did not significantly differ from observed values (χ^2=7.413, df=8,

p=.49). Therefore the predicted rates by the model reliably matched the observed rates of MCI in the sample, and further interpretation of regression analysis was possible.

3.4.3. Relation of FRS to MCI

FRS at Wave 6 predicted 5 year follow up MCI (b=.101, $\chi^2(1)$=19.599, p<.001, OR=1.106, 95% CI OR: 1.058-1.157). The odds ratio can be interpreted such that for every 1 point increase in FRS the odds associated with MCI increased by 10.6%.

3.5. ASCVD Risk Score and MCI

3.5.1. Sample

A logistic regression analysis was done to predict possible MCI at 5 year follow up from ASCVD risk score. Six hundred and seven participants were included in the analysis, with 95 (15.7%) having possible MCI. The sample had a mean ASCVD risk score of 15.29% (SD=16.32%) and a range of 0-85. Recall that ASCVD risk score is represented as an estimated % of an arteriosclerotic event and therefore can only possibly range from 0 to 100. The distribution of ASCVD risk score was skewed, but a normal distribution is not a required assumption of logistic regression. Figure 12. displays the frequency of ASCVD risk in the sample. Because the ASCVD algorithm includes the majority of the basic model covariates utilized in this study, including age, sex, and ethnicity, only years of education was added to the model as a covariate.

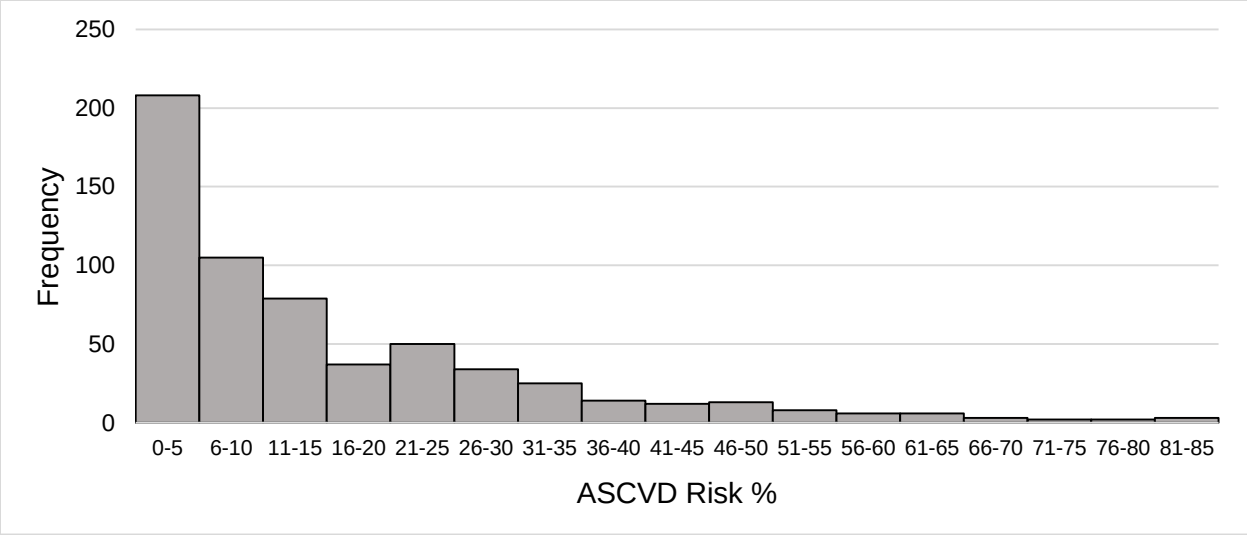

Figure 12. Frequency of ASCVD Risk Scores

3.5.2. Model Fit

A Hosmer and Lemeshow test for model fit determined that the MCI values predicted by the model did not significantly differ from observed values (χ^2=3.701, df=8, p=.88). Therefore the predicted rates by the model reliably matched the observed rates of MCI in the sample, and further interpretation of regression analysis was possible.

3.5.3. Relation of ASCVD Risk to MCI

ASCVD Risk score at Wave 6 predicted 5-year follow up MCI (*b*=.039, χ^2(1)=39.103, p<.001, OR=1.039, 95% CI OR: 1.027-1.052). The odds ratio can be interpreted such that for every 1% increase in ASCVD risk the odds associated with MCI increased by 3.9%.

3.6. Comparison of CV Risk Scores in Predicting MCI

3.6.1 Strategy

The sample was limited to only participants who had complete data for the CVRFS, the FRS, and the ASCVD risk score (N=581). It is important to note that each scale represents a different unit of measurement. The MSLS-CVRFS represents entire

risk factors and had a mean of 2.65 (SD=1.70). The FRS is represented in an algorithmically derived score and had a mean of 12.87 (SD=5.51). The ASCVD risk score is represented as an algorithmically derived percentage and had a mean of 15.35% (SD=16.49%). While it is possible to represent FRS as a risk percentage like the ASCVD risk score the scoring algorithm is capped at 30% risk which is a level of truncation we decided against in order to maintain variance in the distribution of scores. The ASCVD risk score has not been adapted to a simple point scoring system like the FRS and therefore it was necessary to use the percentages produced by the algorithm. While this disparity in units of measurement complicates any interpretation of a comparison between the three scores in predicting MCI, we still feel it is of value to see how each score performs at predicting MCI in identical samples. Because of the varying degrees to which these scales include the demographic variables employed in this study's basic covariate model (age, sex, education, ethnicity), these comparisons will be done as a zero-order logistic regression analysis.

3.6.2. Correlations

The CVRFS, FRS, and ASCVD risk score were all highly positively correlated with each other as can be seen in Table 10. FRS and ASCVD risk score shared the strongest correlation at r=.751 (p<.001), while the CVRFS and ASCVD risk shared a comparatively weaker but still significant positive correlation of r=.271 (p<.001).

Table 10. CV Risk Scores Correlations (n=581)

	CVRFS	FRS	ASCVD
CVRFS	1	.501*	.271*
FRS	.501*	1	.751*
ASCVD	.271*	.751*	1

* p<.05

3.6.3. CV Risk Scores Predicting MCI

All three scores were used in independent zero-order logistic regression analyses to predict 5-year follow up MCI. Hosmer and Lemeshow tests for model fit indicated no significant differences between model-predicted MCI and observed MCI rates for any of the three models, allowing for further interpretation of the regression coefficients. Table 11. displays the regression coefficients and odds ratios for each of the three risk scores. The best statistic for comparison of the three models given the difference in units are the adjusted R^2 values, although interpretation of R^2 in a logistic regression should be done with caution (Hosmer & Lemeshow, 1989). Despite this caution, it is clear that while all three risk scores were significant predictors of MCI at follow-up, the ASCVD outperformed the CVRFS and the FRS in terms of percent variance in MCI explained.

Table 11. Comparison of CV Risk Scores Predicting MCI (n=581)

Risk Score	b	$\chi^2(1)$	p	OR	95% CI (OR)	Nagelkerke R^2
CVRFS	0.165	6.502	0.011*	1.18	1.039 : 1.339	0.019
FRS	0.104	20.412	<.001*	1.11	1.061 : 1.161	0.065
ASCVD	0.039	40.018	<.001*	1.039	1.027 : 1.052	0.115

* p<.05

3.7. Cardiovascular Risk Factor Scale and Cognitive Composite Scores

3.7.1. Sample

A series of linear regression analyses was done to predict continuously distributed cognitive composite scores at 5 year follow up from number of risk factors on the CVRFS. These analyses employed the same five-hundred and ninety subjects included in the logistic regression analysis in Section 3.3. Appendix C displays the

cognitive composites and the factor analyzed cognitive tasks that are included in each composite score (z-score standardized).

3.7.2. Relation of CVRFS to Cognitive Composite Scores

Table 12. displays the results of the series of linear regressions predicting the cognitive composite scores from CVRFS score with and without adjustment for the basic model covariates of age, sex, education, and ethnicity. CVRFS score was negatively associated with every composite score in a zero-order regression analysis ($p<.001$) with a model R^2 ranging from 3.5% to 8.6%. The CVRFS was negatively associated with every composite score in a basic model regression analysis ($p<.01$) with the exception of Verbal Memory ($p=.089$). Model R^2 for the basic model regressions ranged from 25.1% to 51.7%. Figure 13. displays CVRFS plotted against 5-year global composite follow-up score. A quadratic and cubic trend line fit was tested in addition to a linear model, and in some cases a cubic trend resulted in an increase in explained variance of 1-1.5%. Appendix D contains additional plotted trends for the CVRFS and each of the cognitive composites.

Table 12. Linear Regression Analysis Predicting Wave 7 Cognitive Composite Scores from CVRFS Score

	Zero - Order				Basic Model Adjustment			
Outcome	*b*	p	95%CI (b)	Model R^2	*b*	p	95%CI (b)	Model R^2
Verbal Memory	-0.112	<.001*	-.160, -.065	0.035	-0.037	0.089	-.079, .006	0.317
Visual Organization and Memory	-0.133	<.001*	-.179, -.087	0.052	-0.051	.008*	-.089, -.014	0.428
Scanning and Tracking	-0.152	<.001*	-.199, -.105	0.064	-0.06	.001*	-.096, -.024	0.504
Working Memory	-0.172	<.001*	-.218, -.127	0.086	-0.106	<.001*	-.149, -.063	0.251
Executive Functioning	-0.149	<.001*	-.196, -.101	0.061	-0.068	.001*	-.109, -.027	0.354
Global	-0.171	<.001*	-.217, -.125	0.082	-0.076	<.001*	-.111, -.041	0.517

* p<.05

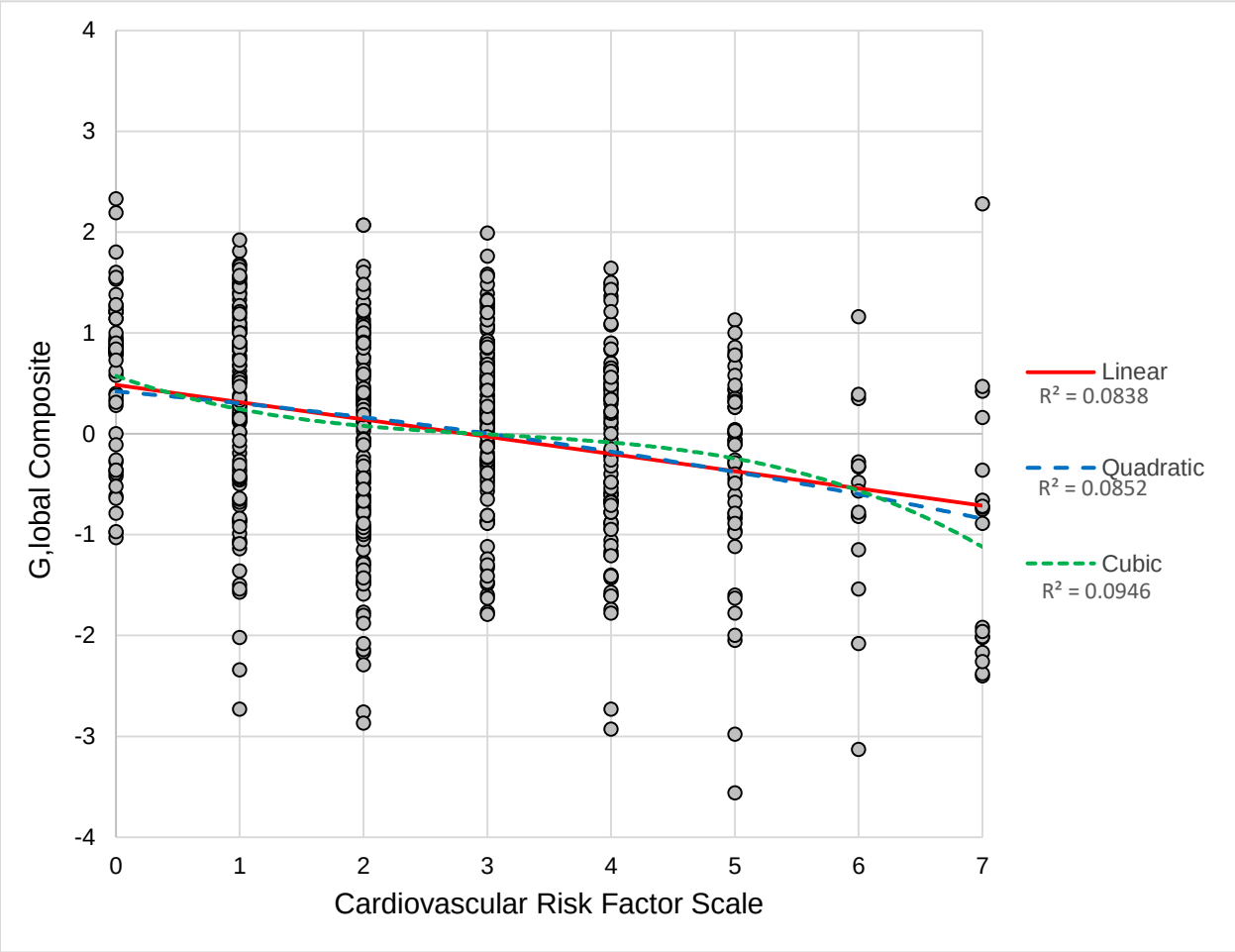

Figure 13. CVRFS Score and Global Composite

4. DISCUSSION

The purpose of this study was to provide new information for the role of cardiovascular risk factors in the prediction of MCI. Of particular interest was examining cardiovascular risk factors that are not well represented in MCI studies. In the first phase of the study, individual risk factors were related to MCI. In the second phase of the study, a cardiovascular risk scale was constructed and used as a predictor of incidence (new cases after baseline) of MCI. The scale was based on a combination of risk factors representing general cardiovascular health (MSLS-CVRFS; see section 2.5.1.). The MSLS-CVRFS was compared to other cardiovascular risk scores used to predict cardiovascular-related mortality and disease incidence.

It has long been known that cardiovascular risk factors and diseases can have a negative impact on brain function and structure and thus influence cognitive function at all ages (Lertiz, McGlinchey, Kellison, Rudolph, & Milberg, 2012; Waldstein & Elias, 2015). There have been many studies examining risk factors and cognitive function (See Section 1.2.). However there are much fewer studies associating cardiovascular health with MCI specifically, especially using cardiovascular risk scores or an aggregate score like the MSLS-CVRFS used in the present study. Because MCI is becoming an epidemiologically and clinically significant disease state in the progression of dementia, it is critically important for studies to identify modifiable risk factors for this condition. Several analyses were conducted in this study in an effort to use the MSLS to address some of the gaps in the MCI literature with regard to specific risk factors like GFR and THCY, as well as cardiovascular risk scores.

4.1. Overview of Findings

4.1.1. Cardiovascular Risk Factors

Nine cardiovascular risk factors (SBP, TC, HDL, LDL, TRIG, GFR, THCY, Diabetes, and PWV) were used to predict MCI over a 5-year follow up period of the present study. Several of these risk factors have not been extensively studied in their relation to MCI prospectively including GFR, THCY, and PWV. Several others were included in the study in an effort to add support to previous findings relating cardiovascular risk factors and MCI: TC, HDL, SBP and diabetes. All of these risk factors were assessed not only for their individual contribution to MCI risk, but for any possible interactions with APOE genotype given the importance of genetic influences on cognitive function. This section discusses results for each risk factor separately in the context of the study hypotheses and related studies from the literature.

In agreement with original hypotheses, GFR was identified as a positive risk factor for MCI. Higher GFR, reflecting healthier kidney function, was protective against MCI. This finding complements the inverse relationship commonly observed between GFR and continuous cognitive functioning (Elias et al., 2009; Kurella, Chertow, Luan, & Yaffe, 2004; Kurella, Yaffe, Shlipak, Wenger, & Chertow, 2005; Slinin et al., 2008) but the results of the present study provide evidence that GFR can predict MCI, a discrete and important clinical outcome. Although kidney function has been associated with risk for dementia (Seliger, 2004), and there is some recent cross-sectional evidence that GFR and MCI are related (Zammit, Katz, Zimmerman, Bitzer, & Lipton, 2015), very few studies have associated kidney function and GFR with MCI prospectively. Mechanisms underlying these relations were not examined in the present study, but there is some

evidence suggesting kidney function can affect arterial compliance (elasticity and responsivity), and this loss of hemodynamic efficiency can be very damaging to the small vessels in the brain (See Section 4.3.).

Elevated THCY was identified as a potential risk factor for MCI, although a statistically significant association was not seen with control for basic demographic variables, most notably age. This negative association is of interest because THCY has been associated with dementia and cognitive impairment no dementia (CIND; a conceptualization of MCI) and this association was moderated by vitamin B12 treatment such that those with higher vitamin B12 levels had lower risk compared to those with lower B12 levels (Mary N. Haan et al., 2007). The contribution of THCY to AD risk may be particularly strong, with results from the Framingham study finding showing a doubled risk of AD (OR=1.8) in patients for every one standard deviation increase in THCY (Seshadri et al., 2002). Homocysteine may play a role in brain health by means of endothelial dysfunction via oxidative stress, increasing the risk of vascular damage. The damaging effects of hyperhomocysteinemia may contribute to increased risk of MCI and dementia (including VaD and AD), but to date lowering of THCY with B vitamin treatments has shown little efficacy in reversing or slowing cognitive decline associated with these diseases.

Pulse wave velocity studies undertaken in the present research were not funded by NIH prior to MSLS wave 7 and thus could not be assessed as a prospective predictor of MCI. However, the current study presents some cross-sectional evidence that arterial stiffness is related to MCI risk by confining our analyses to Wave 7 where it was available as a predictor variable. Subjects diagnosed with MCI exhibited higher PWV,

although this result was not statistically significant with adjustment for age. In another study with a higher average age than the present study (78.0 compared to 66.7 in our study at Wave 7), PWV was shown to be elevated in patients with dementia (AD or VaD) and with MCI compared to CN patients (Hanon et al., 2005). It is important that arterial stiffness be examined in relation to MCI in larger studies. Arterial stiffening occurs naturally with age but can also occur as a result of pathological atherosclerotic processes and it may be a primary mechanism involved in the relation of cardiovascular health to the brain. Interestingly, PWV has previously been associated with cognitive impairment even in healthy populations (Pase et al., 2010; Scuteri et al., 2007; Scuteri, Brancati, Gianni, Assisi, & Volpe, 2005). This may reflect the potential for arterial stiffness to damage brain areas via a reduction in hemodynamic efficiency (O'Rourke & Safar, 2005).

We now consider our results for cholesterol. Most notable among the current study's results for serum lipids was HDL cholesterol's role as a potent positive factor protecting against MCI risk. HDL has been reported previously as a protective factor with regard to cognitive decline and cardiovascular disease (Crichton, Elias, Davey, Sullivan, & Robbins, 2014b; Reitz et al., 2008), but evidence for it as a protective factor against MCI risk is has been sparse prior to the present study. No relationship was found between TC, LDL, and TRIG with MCI, which supports some previous findings (Reitz, 2008). As noted earlier, the importance of this finding for MCI in the present study is that it is a clinically defined outcome that allows yes or no treatment decisions, an essential requirement in medical diagnosis and disease management (Evans, 1988).

SBP was shown to be a risk factor for MCI in the current study in zero order analyses, but not with adjustment for age. The history of hypertension and cognitive function is well defined, with many studies providing evidence that mid-life hypertension and higher BP levels are associated with cognitive decline in late life (M.F. Elias et al., 2012). Past studies with the MSLS data indicate that blood pressure often has to be combined over multiple waves in order to see associations with cognitive performance (M.F. Elias, Goodell, & Robbins, 2015; M.F. Elias et al., 2012, 1993). The current study takes blood pressure from only one wave of examination like the other cardiovascular risk factors included as predictors. Additionally, the present study has a smaller sample size and used a discrete MCI outcome in comparison to past blood pressure studies from the MSLS that associate hypertension with continuously distributed cognitive function (M.F. Elias et al., 1993). There is also now a fair amount of evidence relating blood pressure and hypertension to MCI specifically (M Kivipelto et al., 2001; O. L. Lopez et al., 2003; Reitz et al., 2007). Reitz et al 2007 specifically found that hypertension predicted all-cause MCI and non-amnestic MCI but not amnestic MCI, which adds to evidence suggesting amnestic MCI may be more associated with AD pathology and non-amnestic MCI may be more associated with vascular pathology. However these distinctions are not conclusive; outcomes for various MCI subtypes are not so easily predicted (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006b) and dementia pathologies (particularly AD and VaD) are often mixed (See Section 1.3.3.)

Diabetes mellitus was identified as a risk factor for MCI in the present study even with adjustment for basic demographics, with higher incidence of MCI seen in subjects

who were diabetic at baseline. This finding is consistent with results reported in several previous studies as diabetes has previously been reported as a prospective MCI risk factor (O. L. Lopez et al., 2003; J. A. Luchsinger et al., 2007) and provides supporting evidence to the claim that there may be a higher incidence of MCI among Type 2 diabetics (Cheng et al., 2012). As is true for hypertension, there is an established literature base relating diabetes to a decline in cognitive function in late life (Bent, Rabbit, & Metcalf, 2000; Cukierman, Gerstein, & Williamson, 2005; D. Knopman et al., 2001; Robbins, Elias, Budge, Brennan, & Elias, 2005). The results of this investigation add supporting evidence for its role in predicting MCI as a discrete disease outcome. Importantly, diabetes has been identified as a strong predictor of dementia risk (Alonso et al., 2009; Lu, Lin, & Kuo, 2009). However not all studies that have explored diabetes and MCI have reported that diabetes is a prospective risk factor for MCI (M Kivipelto et al., 2001; Solfrizzi et al., 2004). These differences among studies including our own may be due to diagnostic criteria used for MCI, which has changed considerably in the last twenty years, and varying follow-up periods.

The presence of an APOE ε4 allele has been associated with poor cardiovascular health outcomes and dementia in previous studies (Lahoz et al., 2001; Saunders et al., 1993). No relations between APOE genotype and MCI, nor any interactions between APOE genotype and the studied cardiovascular risk factors were observed. While this finding did not agree with our original hypothesis, findings from the literature base on APOE and its association with MCI are mixed. Some previous studies have shown that the presence of an ε4 allele is an independent risk factor for MCI (Guo et al., 2010; O. L. Lopez et al., 2003). APOE genotype is generally supported as a risk

factor for cognitive decline and dementia (Alonso et al., 2009; Laurin et al., 2007) by mechanism of exacerbating inflammation associated with cardiovascular risk factors (Farrer et al., 1997; Small et al., 2004). Hypertension and cholesterol have been among the most studied in the interaction of APOE as it pertains to MCI risk, but to date several studies have not supported this relationship (Zambon et al., 2010; Reitz et al., 2007; Toro et al., 2014). Larger population based studies are needed to assess the interaction of APOE genotype and cardiovascular risk factors with respect to MCI risk, as the literature is already quite clear on dementia risk.

4.1.2 Cardiovascular Risk Factor Scales and Risk Profiles

In agreement with our hypotheses, an aggregation of cardiovascular risk factors dichotomized into the MSLS-CVRFS predicted MCI at 5-year follow up. A higher MSLS CVRFS was associated with higher incident MCI. This finding is consistent with both the commonly used FRS and the recently developed ASCVD Risk Score, which were also associated with incident MCI. While these established risk profiles (FRS and ASCVD) have shown great success in predicting risk for CVD, their use in predicting other conditions related to cardiovascular health is largely unstudied. In the current study we provide evidence that each of these cardiovascular risk scores can be used to predict an increased risk of incident MCI.

One important contrast between the MSLS-CVRFS and the FRS/ASCVD risk scores used for comparison is that the scale developed in this study does not include any demographic variables such as age and sex. The intent of the MSLS-CVRFS was to focus on cardiovascular risk factors alone, and therefore, we chose to consider age as an important demographic covariate rather than as a cardiovascular risk factor. In

keeping with theoretical conceptions in advancing age in the life-span psychology literature, our conceptualization of chronological age is as a variable representing an exposure time in which the prevalence and incidence of CVD is taking place (See Schroots & Birren, 1990; Settersten & Mayer, 1997). In this life-span perspective, chronological age should be considered an “empty variable” with no force of its own, but which encapsulates the combined effect of countless other variables over time. Although the FRS and the ASCVD performed slightly better in predicting MCI (See Section 3.6.3.) it is important to note that these scales include age, which is arguably the single most important risk factor for MCI and clearly the strongest predictor of dementia. For reference, the baseline age in our study accounted for an estimated 11% of the variance in follow-up MCI when examined separately. This alone was comparable to the estimated percent variance explained by the entire FRS and ASCVD scores (See Section 3.6.3). Notably, the FRS and ASCVD risk score also include sex as a factor, which has been previously reported as an important risk factor, with MCI occurring more frequently in men (R. Petersen et al., 2010). These are not criticisms of the risk models as these scores were developed to predict CVD with as much accuracy as possible, rather than with the intention of elucidating the exact role of certain risk factor mechanisms in the development of CVD. In contrast, with the CVRFS we attempted to model the contribution of cardiovascular risk factors to MCI risk while controlling for the demographic variables included in the other risk scores. Our results do indeed provide evidence that cardiovascular risk factors play a role in this risk. When the CVRFS was modeled with age and sex included as covariates the total model predicted an estimated 15% of the variance in follow-up MCI, which compares favorably to the

percent variance accounted for by the other risk scores. Table 13. summarizes model R^2 values for predicting MCI based on how age was handled as a variable.

Table 13. Summary comparing Model R^2 predicting MCI from Risk Factor Scales

Scale/Measure	Age included in scale	Age included in model as covariate	Model R^2
MSLS-CVRFS	No	No	2%
MSLS-CVRFS	No	Yes	15%
FRS	Yes	No	7%
ASCVD	Yes	No	12%
Age alone	N/A	N/A	11%

These results of the present study have shown promise in the use of cardiovascular risk profiles to predict MCI, despite the fact that these profiles are specifically tailored to predict CVD events, with the exception of the MSLS-CVRFS. This is not the first study from the MSLS to support the value of risk profiles in predicting cognitive impairment; the Framingham Stroke Risk Score was previously shown to predict cognitive functioning by Elias and colleagues (2004), albeit the study focused on individual cognitive outcomes and not MCI. These findings are important considering the large literature base for the role of the cardiovascular system in brain integrity and function. Although originally developed to predict CVD outcomes, these results show that cardiovascular risk scores can also be utilized to predict MCI risk. Our findings have particular relevance to patient treatment strategies because the information used to develop these risk scores (BP, cholesterol etc.) is routinely obtained in physician offices when a metabolic series is performed. It is clear from the present study that a scale employing an aggregation of risk factors is a better predictor of MCI than individual risk factors, and this information is easily obtained from physical examination, patient history, and metabolic profile.

To our knowledge only one study has developed a risk score specifically tailored to predicting MCI risk. Researchers from the Mayo Clinic Study of Aging have recently published a risk scoring system specifically for MCI (Pankratz et al., 2015). The variables in this scale include both demographic and cardiovascular health variables, including sex, years of education, hypertension, and diabetes, among others. The model includes little influence from current age, as it is intended to predict future MCI incidence based on mid-life cardiovascular health and demographics. As is commonly done, age was incorporated in the model as a factor of exposure time to risk factors. Although this risk factor profile shows promise emerging from a study that has been heavily involved in the development of the construct of MCI, further validation in different study populations is necessary.

One of the issues in all risk factor scales that employ age is that age is a powerful predictor of MCI and cognitive performance and can obscure the role of other risk factors. Scales employed by epidemiologists employ age from an entirely empirical perspective in order to maximize prediction. Our primary scale (MSLS-CVRFS) excluded age based on the conceptualization of age as an empty variable in order to focus on the contribution of cardiovascular risk factors to MCI risk. As discussed above, regardless of whether one includes or excludes age in a risk factor scale, risk factor scales combining multiple measures predict MCI better than individual risk factors.

4.2. Summary

In this MSLS sample cardiovascular risk factors predicted MCI in a 5-year prospective analysis. This included blood pressure, GFR, HDL cholesterol, THCY, Diabetes and PWV (cross-sectional). Of these associates GFR and HDL were

particularly strong predictors of MCI risk, with higher levels predicting lower MCI incidence independent of age, sex, education, and ethnicity. While we expected more risk factors to predict MCI it was evident that a combination of risk factors as part of a cardiovascular risk factor scale offered better MCI risk prediction.

The MSLS-CVRFS also predicted MCI risk, and this association was seen with adjustment for age, sex, education and ethnicity. Moreover, the CVRFS was linearly associated with the cognitive composite scores that were used in MCI diagnosis. The FRS for general CVD risk and the recent ASCVD risk score both predicted incident MCI with adjustment for demographic variables that were not included in the score. These findings support the role of cardiovascular risk factors in clinically defined cognitive impairment with older age, and suggest that risk factor scores have more utility than individual risk factors for predicting risk of MCI

4.3. Mechanisms Underlying Cardiovascular Health and Cognitive Function

The current study did not involve an investigation of potential mechanisms underlying the association of cardiovascular risk factors with cognitive functioning. However, it is possible to speculate on these mechanisms based on prior research. The prevailing theory on how alterations in the cardiovascular system can influence cognitive function requires a consideration of the subtypes of cerebrovascular diseases which range considerably in type and severity. Of particular interest is the influence of the cardiovascular system on major white matter neuronal tracts in the brain. These tracts are heavily myelinated neurons responsible for rapid processing speed and communication among different brain regions. Advancements in brain imaging techniques have allowed for the easy detection of white matter damage or degradation,

such as White Matter Hyperintensities (WMH). Manifesting as bright white spots on T2 weighted MRI images, WMHs are often clinically silent regions of white matter degradation possibly due to small vessel diseases. Other microvascular injuries include lacunar infarcts and cerebral micro-bleeds which are similarly asymptomatic.

White Matter Hyperintensities (also known as Leukoaraiosis) have been related to cardiovascular risk factors, cognitive function, and dementia. WMH volume has been associated with the Framingham Stroke Risk Profile as well as several individual cardiovascular risk factors including hypertension, arterial stiffness, kidney function, and diabetes (Fornage et al., 2011; Hughes et al., 2013; Jeerakathil et al., 2004; Khatri et al., 2007; Liao et al., 1997; Longstreth et al., 2005; Skoog, 1998; Van Dijk et al., 2004). In turn WMHs have also been associated with lowered cognitive performance, with executive function impairment commonly seen in patients with high WMH burden (Au, Massaro, Wolf, Young, & Beiser, 2006; Breteler et al., 1994; Carmichael et al., 2010; de Groot et al., 2001; Longstreth et al., 2005). Larger WMH burden is also seen in AD cases, with MCI participants showing WMH levels between those observed in AD and CN participants (Yoshita et al., 2006). It is important to note that white matter volume changes are considered a normal aspect of aging, with volume gradually increasing from birth to midlife, after which volume slowly declines (Kennedy & Raz, 2009). Based on the evidence relating cardiovascular risk factors to WMHs independent of age, it is reasonable to hypothesize that an increase in cardiovascular risk factors may accelerate the lifespan curve of white matter volume and potentially influence cognitive deficits and increased dementia risk.

The literature suggests a similar association among cardiovascular risk factors with lacunar infarctions and cognitive impairment. Also known as lacunar strokes, these cerebrovascular injuries are characterized by small vessel blockages leading to subsequent cell death in deep brain regions represented by small cavities on brain scans. Like a major acute stroke, lacunar infarctions are associated with an increase in cardiovascular risk factors and have been associated with cognitive function and dementia (Mungas et al., 2005; Vermeer, Longstreth, & Koudstaal, 2007). Findings from the Nun Study demonstrated a 20-fold increase in dementia incidence in brains with AD pathology that also had lacunar strokes (Snowdon et al., 1997).

The small cerebral vessels of the cerebrovascular system are susceptible not only to localized disease but also to damaging inputs from the central cardiovascular system. These vessels function somewhat differently from other peripheral vessels. They are constantly in a state of blood perfusion due to lowered vascular resistance as a result of increased vasodilation (O'Rourke & Safar, 2005). This phenomena is in sharp contrast to what takes place in peripheral vessels located in the arms for example, that have much higher vascular resistance and exhibit more vasoconstriction. While the physiology of these cerebral vessels allows for constant blood perfusion to meet the large metabolic demands of the brain, it also makes them particularly vulnerable to damage caused by high pressure waves resulting from a system that has seen a reduction in arterial compliance. Arterial stiffening resulting in higher PWV and pulse pressure may be a primary contributor to this damage, even if the reductions in compliance occur in the central cardiovascular system and not the cerebral vessels themselves, which are often spared from atherosclerotic processes.

While there is an abundance of evidence suggesting a mechanistic association between cardiovascular risk factors and cognitive functioning by way of small vessel diseases and central hemodynamics, there is an additional issue that needs to be addressed. If this mechanistic relation is hypothesized, it should stand to reason that treatment of the cardiovascular risk factors should lower the extent of cerebrovascular injury and therefore improve or prevent cognitive decline including MCI and Dementia. The evidence supporting this hypothesis is mixed. Some reviews and studies have suggested that early treatment of cardiovascular risk factors like hypertension reduces dementia risk (M.F. Elias et al., 2012; Forette et al., 2002). However, most of these treatment interventions have been oriented at prevention of cerebrovascular damage and cognitive impairment to begin with. Importantly, no studies have shown concrete evidence that these outcomes are completely reversible by treating cardiovascular risk factors, despite arguments that they are modifiable. Nevertheless the pursuit of viable treatment interventions for cognitive impairment associated with cardiovascular health is a critical objective in the study of MCI and dementia and should be a large focus of future studies.

In summary, while we did not perform studies allowing us to identify mechanisms in this investigation there is a strong literature base implying the role of central cardiovascular risk factors in cognitive performance by means of cerebrovascular damage. The MSLS will be unable to pursue mechanistic investigations further, but we encourage other studies to consider investigating underlying mechanisms relating cardiovascular health to MCI.

4.4. Study Limitations and Strengths

4.4.1. Limitations

While the current study provides important new data on cardiovascular risk factors in relation to MCI, several limitations should be considered. This study used an archival diagnosis of MCI that was derived from a full neuropsychological assessment supported by various medical and social assessments. Here we use the term “archival” to define a diagnosis that is based on existing data from the MSLS and does not include further correspondence with the patient. For compliance with privacy protection and approved MSLS human subjects research protocol we are blind to who the patients are. Archival diagnosis can be difficult, and care must be taken to apply diagnostic criteria as rigidly as possible with all relevant data available. Furthermore, archival diagnosis is limited in comparison to direct contact with the individual as would be the case in a clinic setting. However, in order to make the diagnosis of MCI as accurate as possible we strictly adhered to the primary principles of MCI diagnoses outlined in Section 1.4.2.

In accordance with these principles a participant in the MSLS had to exhibit a decline from previous cognitive function to a sufficient degree, be free from dementia, and be able to function independently in their everyday life. The MSLS includes data relevant to all of these principles, and we were therefore able to retrospectively identify subjects that fit this well-established MCI profile. Furthermore, a stricter definition for cognitive decline was utilized in the current study in order to limit false positive diagnoses. This same approach was taken in the Framingham studies of dementia (M F Elias et al., 2000). Importantly, the MSLS neuropsychological battery is comprehensive and extensive, and therefore, we were also able to consider all possible cognitive

decline phenotypes that may represent MCI, including single and multi-domain impairment.

While seven waves of data have been collected in the MSLS since 1975, the current study was limited to a 5-year follow-up period because some cardiovascular risk factors of interest (Serum lipids, THCY, GFR) were not available prior to Wave 6 of the study (See Section 2.1.). While other MSLS studies, particularly those using blood pressure and hypertension as primary predictors, have been able to use longer follow-up periods, we feel the current 5-year period is necessary because we are specifically investigating a mid to late life sample who carry the highest risk for MCI diagnosis. It was likewise necessary to maximize the number of cardiovascular risk factors included in the study, and Wave 6 of the MSLS has the largest number of risk factors available.

The MSLS-CVRFS has some shortcomings related to the fact that we lacked the sample size to develop a more sophisticated scale based on continuously distributed cardiovascular risk factors (used in prediction models like the FRS and ASCVD risk score). Both of these prediction models were based on algorithms derived from large datasets. In contrast, in the current study we were restricted to two categories (yes/no) based on current diagnostic standards and counted the number of risk factors to create our scale. This method essentially weighs each risk factors equally in the scale. This method allowed us to consider the role of clinically defined cardiovascular risk conditions to MCI at the cost of some recognition for risk factors that may be just above or below the clinical cutoff points. The MSLS-CVRFS was developed as a research instrument and not a formal psychometric scale, with the intent to study the contribution of a combination of cardiovascular risk factors.

4.4.2. Strengths

Despite the limitations discussed above, the current study has a number of important strengths. To our knowledge this study is the first to relate a cardiovascular risk factor aggregation score to MCI in a prospective design. Additionally, we have further validated the use of cardiovascular risk factor algorithms, such as the FRS and ASCVD, in the prediction of negative health outcomes. Furthermore, like the Framingham risk studies the MSLS sample is a community-based sample with a large number of older adults, rather than patients recruited from clinics or in-hospital.

While our sample is small relative to large studies like the Framingham Heart Studies which often include several thousand participants in an analysis, we have one of the largest test batteries in a NIH funded study with 22 cognitive measures (See Torres, Elias, Seliger, Davey, & Robbins, 2016).The depth of this cognitive assessment is not practical in a large sample typical of an observational study. This extensive cognitive battery is invaluable for investigating decreases in cognitive performance and formed the basis for our MCI diagnosis. The current study utilized all of the available data from the cognitive battery. The analyses in this study were strictly restricted to only individuals who had complete cognitive testing data and attended Wave 6 and 7 of the MSLS.

4.5. Future Directions

MCI has already been established as a clinically defined precursor to dementia. Ultimately, its clinical significance is dependent on how well it predicts transition to dementia because MCI itself is does not interfere with activities of daily living by definition. MCI has met this condition fairly well, albeit different definitions abound.

Regardless of various criteria, when a diagnosis of MCI is made reasonably and empirically based, it predicts much higher transition rates to dementia than are expected in the general population (Larrieu et al., 2002; Petersen et al., 1999; Petersen, 2011). Therefore, two transition periods in the assessment of MCI are of critical clinical importance: The transition from normal functioning to MCI, and the transition from MCI to dementia.

The current study joins several other studies in providing evidence for the important role of cardiovascular risk factors in the transition from normal functioning to MCI. While more studies exploring the role of cardiovascular health in this transition are needed, the second conversion phase from MCI to dementia also requires investigation. More work remains to be done exploring risk factors that may exacerbate the second transition rate from MCI to dementia, with particular attention to cardiovascular risk factors which may contribute to forms of VaD or mixed vascular-Alzheimer's pathology dementia (Merrill F. Elias & Davey, 2009). There are a few studies that have explored this conversion phase, and have provided evidence that certain cardiovascular risk factors including APOE ε4 increase the risk for a transition to dementia (Kryscio, Schmitt, Salazar, Mendiondo, & Markesbery, 2006). More studies are needed, particularly those investigating possible mechanisms such as arteriosclerosis and cerebrovascular disease.

Differential diagnosis of MCI should remain a primary goal in epidemiological studies assessing MCI and dementia risk. These diagnoses can be difficult to make however as cognitive phenotypes displayed in patients with MCI can be incredibly heterogeneous (See section 1.4.). However if these different forms of MCI can be

accurately mapped onto the forms of dementia they specifically predict (e.g. Amnestic Single Domain MCI -> Alzheimer's Disease) it will vastly improve the clinical use of an MCI diagnosis because interventions can be tailored to the specific form of dementia that the patient is at risk of developing. This is particularly relevant for identifying forms of cognitive impairment that may predict mixed forms of vascular and Alzheimer's pathology as these are underrepresented in a field biased towards AD prediction (Sullivan & Elias, 2016).

4.6. Conclusion

The current study contributes to identifying risk factors for MCI, which should be a critical epidemiological goal in the effort to combat increasing dementia rates worldwide. Dementia is an irreversible condition and efforts to address this disease should focus on prevention and delaying onset. Of particular value in this effort will be the identification of modifiable risk factors for which treatment may reduce risk of abnormal or accelerated cognitive decline with age. Cardiovascular risk factors have been associated with cognitive decline and dementia (Waldstein & Elias, 2015), and the current study suggests that they may predict prodromal states of dementia including MCI. Just as patients are advised to treat cardiovascular risk factors in an effort to prevent CVD, the risk of dementia associated with an unhealthy cardiovascular profile should also be considered.

We consider each objective and hypothesis presented in Section 1.7. in turn. While we did see that individual cardiovascular risk factors could predict MCI incidence, most of these associations were lost with control for the basic covariate model. However, this was not the case with GFR and HDL cholesterol, which were associated

with lower MCI risk. Furthermore, diabetes was associated with an increased MCI incidence. Contrary to our hypothesis, no moderating effect of APOE ε4 allele was observed with any risk factor. In agreement with our hypothesis, an aggregation of cardiovascular risk factors, reflected in our CVRFS, predicted higher risk of MCI. Two recommended cardiovascular risk factor algorithms, the FRS and ASCVD risk score, also predicted higher risk of MCI. As originally hypothesized the FRS and ASCVD performed better in predicting MCI than the CVRFS, likely because the former two risk scores include age. Lastly, in agreement with our final hypothesis the CVRFS also predicted continuously distributed cognitive performance measures from the MSLS cognitive battery.

The present study has many implications for predicting MCI using cardiovascular risk factors. Among the individual risk factors we studied, GFR, HDL cholesterol, and diabetes were particularly strong predictors of MCI. However, using a combination of multiple risk factors may prove more useful in predicting MCI risk than any single risk factor, even when age is not accounted for. Patients often come to physicians with multiple cardiovascular risk factors, and these individuals may be more vulnerable to MCI and conversion to Dementia. We find that our MSLS-CVRFS, the scale developed in this study, was more successful in predicting individual cognitive outcomes measured continuously, but the larger importance of this study is in presenting evidence for predicting MCI as a clinically defined disease that demands a yes/no treatment decision from physicians. Predicting this risk is especially useful when it can identify MCI so that interventions can occur long before dementia occurs in an effort to counteract long prodromal phase of dementia. We strongly recommend that future studies associating

cardiovascular risk factor aggregation and individual risk factors with MCI should identify MCI subtypes (amnestic single domain, non-amnestic single domain etc.) in an effort to develop different risk profiles predicting different types of dementia (AD, VaD, Mixed).

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APPENDIX A: FRAMINGHAM RISK SCORE CALCULATION

Table 14. FRS Calculation for Women

Points	Age	SBP (Untreated)	SBP(Treated)	TC	HDL	Smoker	Diabetic
-3		< 120					
-2					60+		
-1			<120		50-59		
0	30-34	120-129		<160	45-49	No	No
1		130-139		160-199	35-44		
2	35-39	140-149	120-129		<35		
3			130-139	200-239		Yes	
4	40-44	150-159		240-279			Yes
5	45-49	160+		280+			
6			150-159				
7	50-54		160+				
8	55-59						
9	60-64						
10	65-69						
11	70-74						
12	75+						

Table 15. FRS Calculation for Men

Points	Age	SBP (Untreated)	SBP(Treated)	TC	HDL	Smoker	Diabetic
-2		<120			60+		
-1					50-59		
0	30-34	120-129	<120	<160	45-49	No	No
1		130-139		160-199	35-44		
2	35-39	140-159	120-129	200-239	<35		
3		160+	130-139	240-279			Yes
4			140-159	280+		Yes	
5	40-44		160+				
6	45-49						
7							
8	50-54						
9							
10	55-59						
11	60-64						
12	65-69						
13							
14	70-74						
15	75+						

Tables and scoring adapted from D’Agostino et al. 2008

APPENDIX B: ARTERIOSCLEROTIC CARDIOVASCULAR DISEASE RISK SCORE CALCULATION

Method: A coefficient sum C is calculated for a patient with a different algorithm based on sex, ethnicity (White vs African American Only), and hypertensive treatment status (Treated vs Untreated). This coefficient sum is then converted to a 10-year risk percentage in a second equation including parameters based on average values (baseline survival rate and average coefficient sum) for that patient's sex and ethnicity.

Coefficient Sum Calculation (C)

Men

White

Untreated: (ln(Age) * 12.344) + (ln(TC) * 11.853) + ((ln(Age * ln(TC)) * -2.664) + (ln(HDL) * -7.990) + ((ln(Age) * ln(HDL)) * 1.769) + (ln(SBP) * 1.764) + (Smoker * 7.837) + ((ln(Age) * Smoker) * -1.795) + (Diabetes * .658) = C

Treated: (ln(Age) * 12.344) + (ln(TC) * 11.853) + ((ln(Age * ln(TC)) * -2.664) + (ln(HDL) * -7.990) + ((ln(Age) * ln(HDL)) * 1.769) + (ln(SBP) * 1.797) + (Smoker * 7.837) + ((ln(Age) * Smoker) * -1.795) + (Diabetes * .658) = C

African American

Untreated: (ln(Age) * 2.469) + (ln(TC) * .302) + (ln(HDL) * -.307) + (ln(SBP) * 1.809) + (Smoker * .549) + (Diabetes * .645) = C

Treated: (ln(Age) * 2.469) + (ln(TC) * .302) + (ln(HDL) * -.307) + (ln(SBP) * 1.916) + (Smoker * .549) + (Diabetes * .645) = C

Women

White

Untreated: (ln(Age) * - 29.799) + ((ln(Age) * ln(Age)) * 4.884) + (ln(TC) * 13.540) + ((ln(Age) * ln(TC)) * -3.114) + (ln(HDL) * -13.578) + ((ln(Age) * ln(HDL)) * 3.149) + (ln(SBP) * 1.957) + (Smoker * 7.574) + ((ln(Age) * Smoker) * -1.665) + (Diabetes * .661) = C

Treated: (ln(Age) * - 29.799) + ((ln(Age) * ln(Age)) * 4.884) + (ln(TC) * 13.540) + ((ln(Age) * ln(TC)) * -3.114) + (ln(HDL) * -13.578) + ((ln(Age) * ln(HDL)) * 3.149) + (ln(SBP) * 2.019) + (Smoker * 7.574) + ((ln(Age) * Smoker) * -1.665) + (Diabetes * .661) = C

African American

Untreated: (ln(Age) * 17.114) + (ln(TC) * .940) + (ln(HDL) * -18.920) + ((ln(Age) * ln(HDL)) * 4.475) + (ln(SBP) * 27.820) + ((ln(Age) * ln(SBP)) * -6.087) + (Smoker * .691) + (Diabetes * .874) = C

Treated: (ln(Age) * 17.114) + (ln(TC) * .940) + (ln(HDL) * -18.920) + ((ln(Age) * ln(HDL)) * 4.475) + (ln(SBP) * 29.291) + ((ln(Age) * ln(SBP)) * -6.432) + (Smoker * .691) + (Diabetes * .874) = C

10-Year ASCVD Risk Percentage Calculation

Basic Formula:

$$1 - \text{Baseline Survival Rate}^{e\hat{}(\text{Patient Coefficient Sum} - \text{Average Coefficient Sum})} = \%\ \text{Risk}$$

Men

White

$$1 - 0.9144^{e\hat{}(C - 61.68)} = \%\ \text{Risk}$$

African American

$$1 - 0.8954^{e\hat{}(C - 19.54)} = \%\ \text{Risk}$$

Women

White

$$1 - 0.9665^{e\hat{}(C + 29.18)} = \%\ \text{Risk}$$

African American

$$1 - 0.9533^{e\hat{}(C - 86.61)} = \%\ \text{Risk}$$

Algorithm adapted from Goff et al. (2014)

APPENDIX C: MSLS COGNITIVE BATTERY AND FACTOR ANALYZED COGNITIVE DOMAINS

Table 16. Descriptions of Cognitive Tests for Each Cognitive Domain

Composite/ Tests included	Cognitive Ability Measured
Verbal Episodic Memory	
Logical Memory-Immediate Recall [a]	Immediate memory, verbal
Logical Memory-Delayed Recall [a]	Delayed Memory, verbal
Hopkins Verbal Learning Test	Verbal learning and memory
Visual-Spatial Organization/Memory	
Visual Reproductions-Immediate Recall [a]	Immediate recall, visual memory and visual spatial problem solving
Visual Reproductions-Delayed Recall [a]	Delayed recall, visual memory and visual spatial problem solving
Matrix Reasoning [b]	Abstract reasoning and pattern recognition
Block Design [c]	Visual-spatial perception, organization
Object Assembly [c]	Speed of visual-spatial organization
Hooper Visual Organization	Visual-spatial organization, some demands on executive function
Scanning and Tracking	
Trail Making A [d]	Visual scanning and tracking; concentration and attention
Trail Making B [d]	Trails A plus demands on executive function abilities
Digit Symbol Substitution [c]	Psychomotor performance
Symbol Search [b]	Visual processing speed
Working Memory	
Digit Span Forward [c]	Attention and concentration
Digit Span Backward [c]	Attention, concentration, and working memory
Letter-Number Sequence [b]	Information processing while holding information in memory
Controlled Oral Word Associations	Verbal fluency and executive function
Executive Function	
Trail Making B [d]	Trails A plus demands on executive function abilities
Controlled Oral Word Associations	Verbal fluency and executive function

[a] Origin Wechsler Memory Scale-Revised
[b] Origin Wechsler Adult Intelligence Scale III
[c] Origin Wechsler Adult Intelligence Scale
[d] Origin Halstead-Reitan Neuropsychological Test Battery

APPENDIX D: ADDITIONAL FIGURES FOR CVRFS AND COGNITIVE COMPOSITE ANALYSES

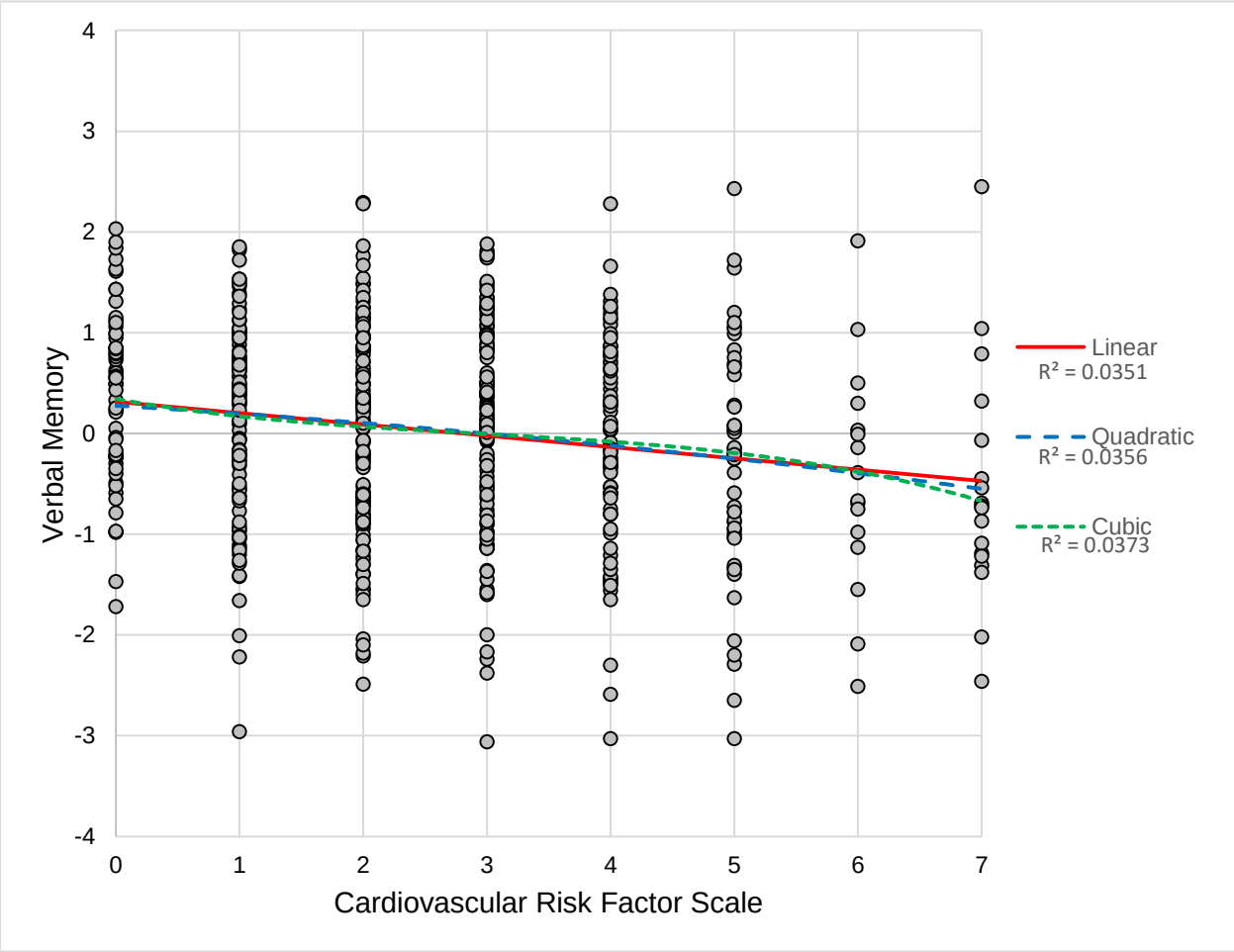

Figure 14. CVRFS Score and Verbal Memory

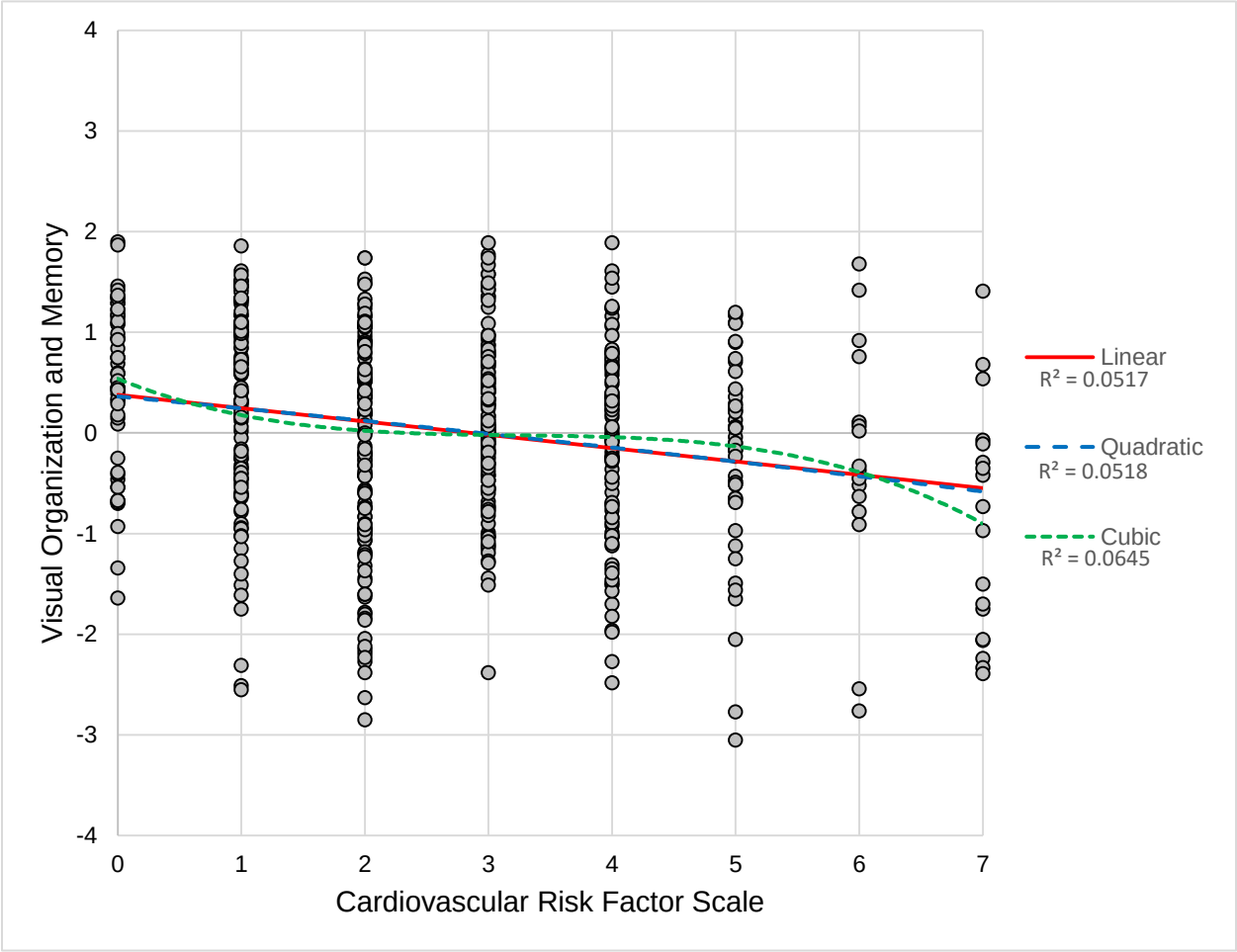

Figure 15. CVRFS Score and Visual Organization/Memory

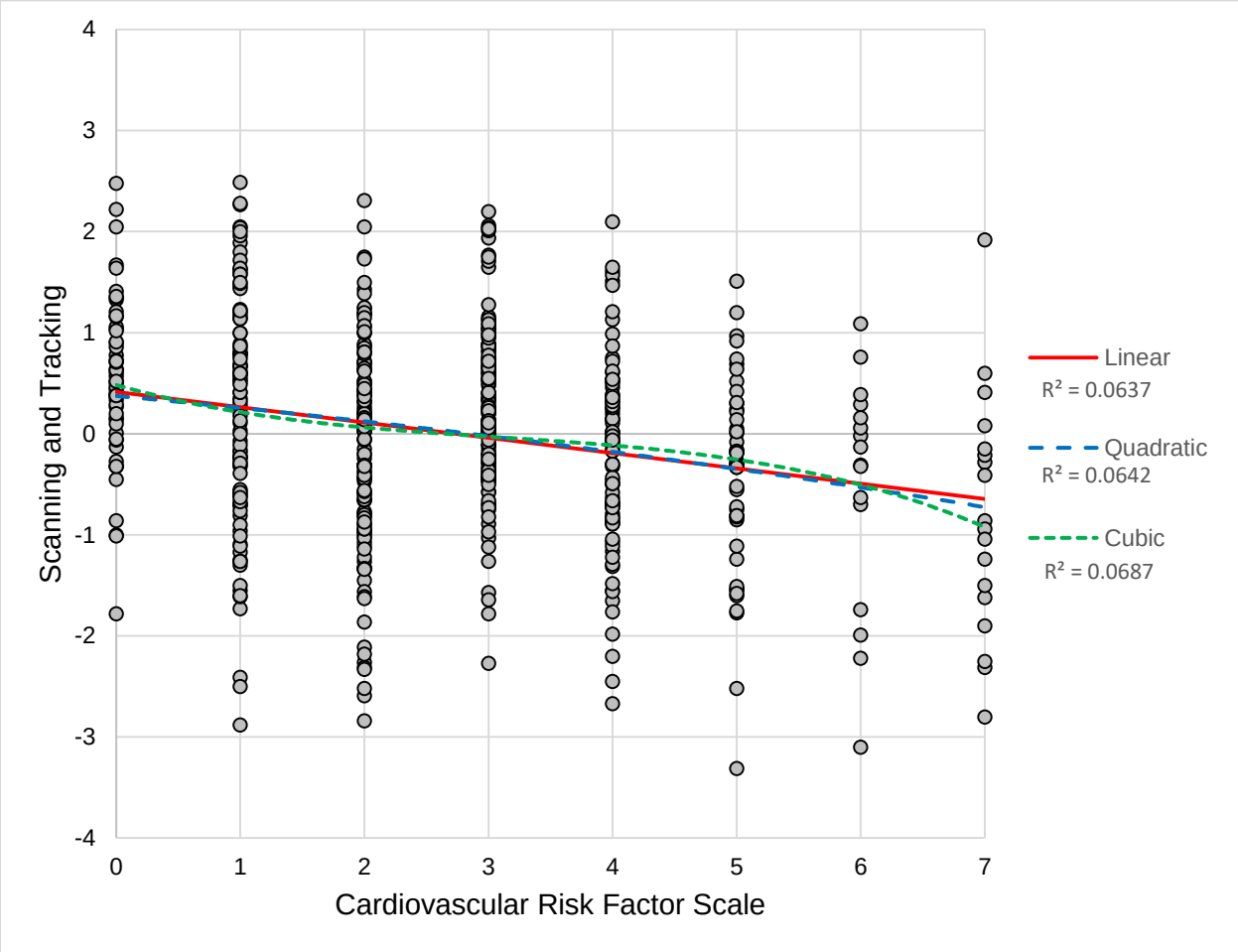

Figure 16. CVRFS Score and Scanning/Tracking

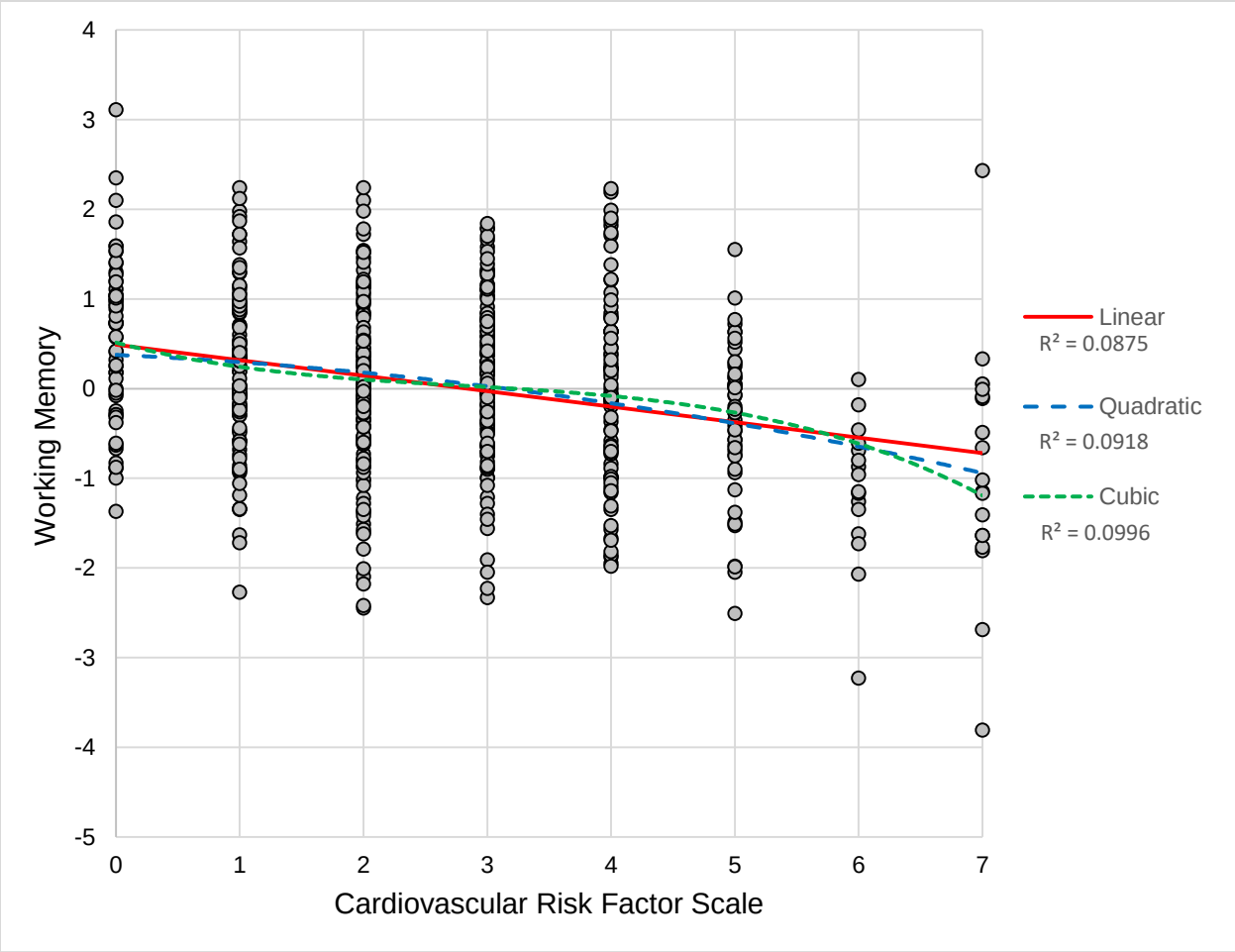

Figure 17. CVRFS Score and Working Memory

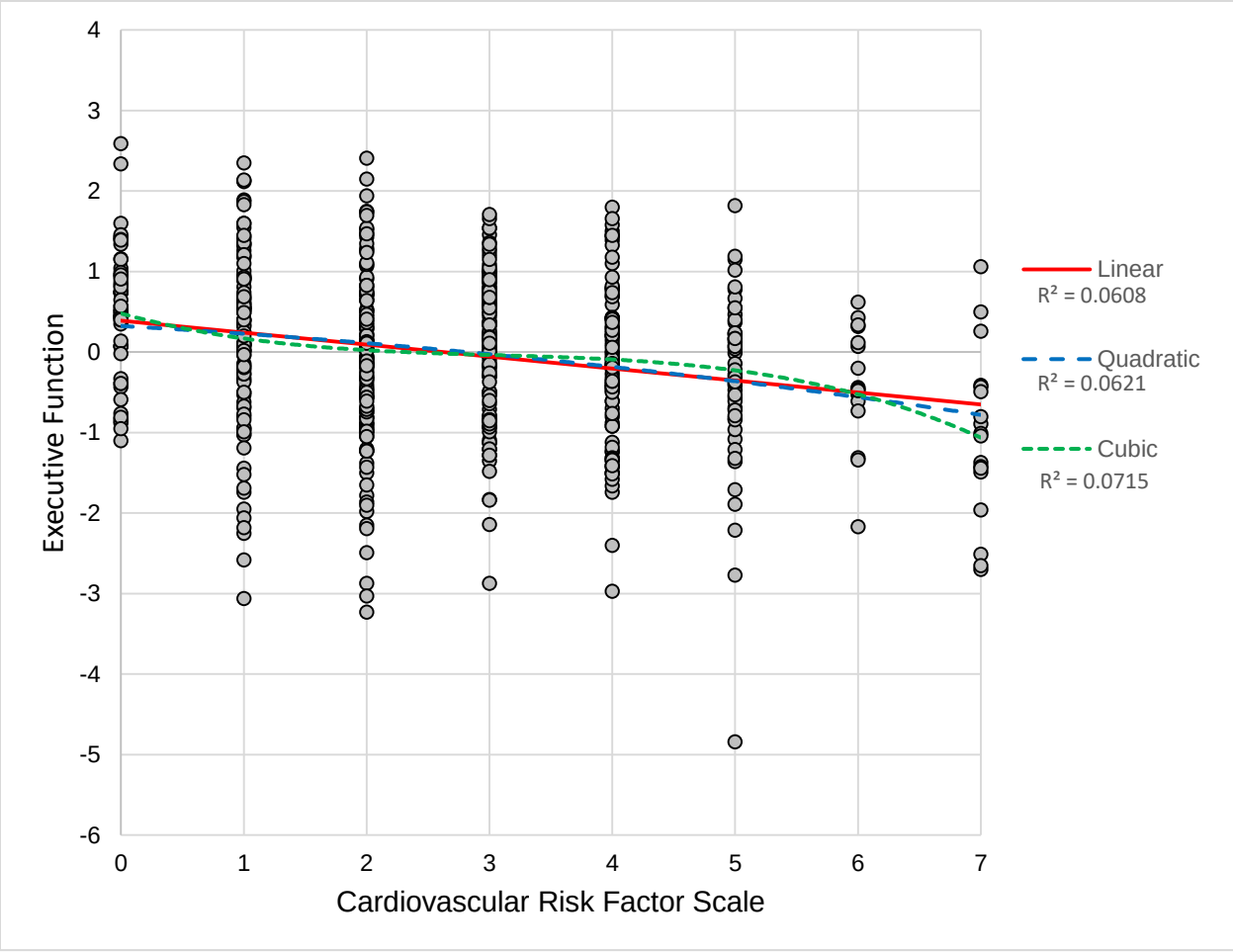

Figure 18. CVRFS Score and Executive Function

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Kevin Joseph Sullivan was born in Bryn Mawr, Pennsylvania on August 12th, 1990. He was raised in Malvern, Pennsylvania and graduated from Great Valley High School in 2009. Kevin received his Bachelor's degree in Psychology from the University of Pittsburgh in 2012, and immediately began his doctoral studies at the University of Maine in the Psychological Sciences program. Kevin joined the Maine-Syracuse Longitudinal Study as a graduate research assistant under co-advisors Dr. Merrill F. Elias (MSLS Principle Investigator) and Dr. Michael A. Robbins. He is a co-author on four peer-reviewed publications and eleven conference presentations. His recent awards include the Janet Waldron Dissertation Research Fellowship and the Chase Distinguished Research Assistantship from the University of Maine Graduate School. He is a candidate for the Doctor of Philosophy degree in Psychology from the University of Maine in August 2017.