Fall 12-15-2017

Prospective Associations of Homocysteine, Executive Function, and Depressive Symptoms

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PROSPECTIVE ASSOCIATIONS OF HOMOCYSTEINE, EXECUTIVE FUNCTION, AND DEPRESSIVE SYMPTOMS

by

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B.A. University of Maine, 2009

A DISSERTATION

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

(in Psychology)

The Graduate School

The University of Maine

December 2017

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An Abstract of the Dissertation Presented in Partial

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Associations of cardiovascular risk factors, cognitive performance, and depressive symptoms have been well established. However, the directionality of these associations as well as the specificity of these associations with respect to executive function are less clear. Additionally few studies have determined whether genetic risk factors, such as apolipoprotein-E4 (APOE-E4) genotype, and age moderate the associations of cardiovascular risk factors such as homocysteine with changes in depressive symptoms and how these associations may be mediated by cognitive performance. The primary aim of this study was to analyze the bidirectional associations of a full range of cognitive domains and symptoms of depression over a period of 5 years and to determine the extent to which the conditional associations of homocysteine (moderated by age and APOE-E4 genotype) and changes in depressive symptoms are mediated by cognitive performance. Additionally, we aimed to determine the extent to which these associations are specific to executive function as compared

with other domains of cognitive function. After exclusions for probable dementia, kidney dialysis, and acute stroke, 719 adult participants were available for analysis for the sixth and seventh waves of the Maine-Syracuse Longitudinal Study. We conducted cross-sectional multiple linear regression analyses and cross-lagged panel analyses (CLPD) to determine the strength and directionality of associations for cognitive function and symptoms of depression. Next, we conducted conditional mediation path analyses to explore the associations of homocysteine (moderated by age and APOE-E4) and changes in self-reported depressive symptoms as mediated by cognitive function. All models were adjusted for wave 6 demographic covariates (age, sex, education, ethnicity, and marital status), cardiovascular risk profile (Framingham Risk Score), and depressive symptoms. In fully adjusted cross-sectional models, depressive symptoms were inversely associated with executive function and several other cognitive domains. In CLPD, cognitive performance was a stronger and more consistent predictor of changes in depressive symptoms (Executive Function, Global performance, Scanning and Tracking, and Visual-Spatial Organization and Memory) than depressive symptoms were of changes in performance. Although cognitive performance largely did not mediate the associations of cardiovascular risk factors (homocysteine and Framingham Risk Score) and changes in depressive symptoms, we did observe direct associations of Framingham Risk Score and changes in symptoms as well as significant moderation by age and APOE-E4 for the associations of homocysteine and changes in depressive symptoms. For APOE-E4 non-carriers, higher homocysteine was associated with symptom increases for individuals ≥ 74.33 years of age and for APOE-E4 carriers, there were marginal risks for individuals ≤ 45 years of age. The findings of this study have

important clinical implications in assessing risk for and prevention of depressive symptoms both via maintenance of cognitive function and CVD risk reduction. Better executive functioning and performance in other cognitive domains was associated with lower levels of depressive symptoms over five years. Lower levels of CVD risk, both for the well-established CVD risk factors indexed by the Framingham Risk Score and for homocysteine, were associated with lower levels of depressive symptoms over five years. Moderation of depressive symptoms may be afforded through interventions designed to maintain executive function and to reduce risk relating to modifiable CVD risk factors such as homocysteine. Clinical trials with patient populations are needed to determine whether modification of homocysteine via dietary or physical activity adjustments could provide effective prevention of depressive symptoms.

ACKNOWLEDGEMENTS

Thank you Professors Michael Robbins and Merrill “Pete” Elias for your unwavering support and guidance and for the opportunities afforded to me from your years of dedicated work on the Maine Syracuse Longitudinal Study. I would like to thank Professor Emeritus, Geoffrey Thorpe for fueling my intellectual and statistical curiosities in my early days as an undergraduate. Also great thanks to Professor Emily Haigh for her continued collaboration during my transition to psychological sciences and Professor Craig Mason for his statistical expertise and for inspiring the design of this dissertation. Thanks to my wife Alden, whose love is constant in a world of variability and error. Lastly, thank you to my mom for being my earliest scientific exemplar and to my dad for showing me the values of patience and of work well done.

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
APOE	apolipoprotein
BMI	body mass index
BD	Block Design
B6	pyridoxine
B9	folate
B12	cobalamin
CES-D	Center for Epidemiological Studies – Depression
CFI	confirmatory fit index
CI	confidence interval
CLPD	cross-lagged panel design
COWA	Controlled Oral Word Association
CVD	cardiovascular disease
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
EF	Executive Function
FTD	frontotemporal dementia
Hcy	homocysteine
HDL	high density lipoprotein
ICD-10	International Classification of Diseases
LDL	low density lipoprotein
MCI	mild cognitive impairment
MRI	magnetic resonance imaging

MDD	major depressive disorder
MDE	major depressive episode
MMSE	Mini Mental State Exam
MR	Matrix Reasoning
MSLS	Maine-Syracuse Longitudinal Study
NINDS-AIREN	National Institute of Neurological Disorders and Stroke criteria
RMSEA	root mean squared error of approximation
ST	Scanning and Tracking
tHcy	total plasma homocysteine
VaD	vascular dementia
VEM	Verbal Episodic Memory
VSOM	Visual-Spatial Organization and Memory
WAIS-R	Wechsler Adult Intelligence Scale – Revised
WAIS-III	Wechsler Adult Intelligence Scale-III
WM	Working Memory
WMS-R	Wechsler Memory Scale-Revised
WHO	World Health Association
WMH	white matter hyperintensities
ZDI	Zung Depression Inventory

1. INTRODUCTION

Human cognitive and emotional development is rapid in early life, but it is well known that changes continue to occur throughout adulthood and into later life. One influential cognitive aging model distinguishes between total fund of world knowledge (i.e., crystalized), which tends to remain stable in older adulthood and abilities relating to speed and power of decision-making (i.e., fluid), which tends to decline with aging (Glisky, 2007; Harada, Natelson Love, & Triebel, 2013; Horn & Cattell, 1967). It is also well known that cognition and emotion regulation have considerable overlap at every age (Hammar & Ardal, 2009). Successfully coping with novel events and stressors requires both the ability to regulate emotion and the ability to select, plan, initiate, and reevaluate appropriate behavioral actions. However, despite some overlap between cognitive ability and depressive symptoms, not all individuals with high levels of depressive symptoms have low cognitive ability and not all of those with low cognitive ability experience high levels of depressive symptoms, which have led many researchers to examine what risk factors may be common to both conditions.

Interest continues to grow with regard to the vascular risk factors that are common among older individuals with cognitive deficits and depressive symptoms and there is an expanding literature on the possibility that vascular mechanisms underlie the relationships between cognitive decline and depressive symptoms. Prevention and reduction of vascular risks through lifestyle changes and pharmacological treatment may not only reduce the medical burden posed by cognitive decline and symptoms of depression, but may also result in a lifespan compression of overall morbidity and dependent/institutional living.

In Section 1.1, we review different measurements of depressive symptoms (Section 1.1.1), depressive symptoms and aging (Section 1.1.2) and the vascular depression hypothesis (Alexopoulos et al., 1997; Section 1.1.3). In Section 1.2, we highlight two vascular risk factors of interest: homocysteine (Section 1.2.1) and Apolipoprotein E genotype (Section 1.2.2).

In Section 1.3 we discuss the measurement and course of cognitive performance and the prevalence of cognitive impairment (Section 1.3.1) and its relationship with executive function, vascular disease, and homocysteine (Sections 1.3.2 to 1.3.4). We then discuss how executive function, aging, and symptoms of depression may be related (Section 1.4) by summarizing the literature on depression-executive dysfunction syndrome (Section 1.4.1) and, possible directional associations of depressive symptoms and cognitive performance/executive function. We close chapter 1 by proposing possible mechanisms of cognitive decline (1.4.2 to 1.4.3).

In this study, we first aim to expand upon the vascular depression hypothesis by observing how performance across several cognitive domains may predict changes in depressive symptoms over time. After exploring the temporal connection between cognitive performance and depressive symptoms, we analyze whether cardiovascular risk factors such as age, APOE-E4 genotype, and homocysteine interact to predict changes in symptoms of depression through their associations with cognitive performance.

1.1 Symptoms of Depression

Episodes of major depression are characterized by a wide range of persistent affective, behavioral, and cognitive symptoms. There are two main competing diagnostic systems currently in use, the World Health Organization's International Classification of Diseases (ICD-10; WHO, 2016) and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013). Although there is some difference with regard to the specific word choice for describing diagnostic criterion, the DSM-5 and the ICD-10 overlap considerably regarding the diagnosis of an episode of Major Depressive Disorder (MDD). Specifically, MDD is characterized by persistent dysphoria and loss of interest/pleasure in daily activities and may include any of the following symptoms: disturbance in sleep/weight/appetite/psychomotor activity, fatigue, feelings of guilt/worthlessness, diminished ability to concentrate or make decisions, and thoughts of suicide. In both the ICD-10 and DSM-5, individuals with MDD may be further subdivided into Mild, Moderate or Severe categories based on symptom count and severity, but they are ultimately categorical taxonomies. These systems provide useful heuristics for binary treatment decision-making, but evidence from community-based population studies suggests that unipolar depression is more likely to be a dimensional construct with a continuum of related symptoms found among all individuals (Prisciandaro & Roberts, 2005). This is important because individuals often experience similar levels of functional impairment despite being just below a diagnostic threshold (Prisciandaro & Roberts, 2005). The next section will discuss both the diagnostic prevalence of MDD as well as the phenomenology of symptoms of depression in older compared with younger adults.

1.1.1 Symptoms of Depression and Aging

MDD is one of the most common mental health disorders in the United States. In 2014, approximately 15.7 million adults (6.7%) experienced at least one Major Depressive Episode (MDE) in the past 12 months. Compared with younger (9.3%) and middle-aged adults (7.2%), older adults (5.2%) are estimated to have a lower 12-month prevalence rate of MDE (Center for Behavioral Health Statistics and Quality, 2015). However, lower estimates of MDD among older adults may be systematically biased by the association between MDD and early mortality (Blazer, 2009). Additionally, older adults (≥ 65y) are less likely to identify a range of symptoms of depression (i.e., sadness, guilt, thoughts of suicide, motor slowing, trouble concentrating, and insomnia) compared with younger adults (< 65y; Wetherell et al., 2009). Current diagnostic systems also prioritize dysphoria which is less commonly endorsed by older adults compared with younger adults (Hegeman et al., 2012).

However, despite a general decreasing trend for depressive symptoms in the transition from middle to later adulthood, older adults are at an increased risk for experiencing a number of conditions associated with depression. For example, symptoms of depression are common among those recovering from myocardial infarction, stroke, and hip fractures or suffering from diabetes, arthritis, and kidney disease (Blazer, 2009). Additionally, institutional living, lack of social support, bereavement, functional impairment and loss of economic power are also more common, especially among the oldest old and contribute a significant level of risk for depressive symptoms (Blazer, Burchett, Service, & George, 1991; McDougall, Matthews, Kvaal, Dewey, & Brayne, 2007). Sleep disturbance, subjective memory

complaints, fatigue, and motor slowing, which are more common among depressed older adults, may be misconstrued as conditions associated with normal aging, medication use, or general medical ailments (Fiske, Wetherell, & Gatz, 2009).

Although the risk for future depressive episodes is considerably greater for those with a history of MDD (Burcusa & Iacono, 2007), as many as half of older adults with MDD experience the condition as a first episode (Brodaty et al., 2001). Most studies define "late-onset depression" as experiencing an initial depressive episode after the ages of 50 – 65 (Blazer, 2009; Driscoll et al., 2005; Fountoulakis et al., 2003; Mahapatra, Sharma, & Khandelwal, 2015). Evidence suggests that among older adults, those with early or late-onset depression exhibit similar levels of severity and diagnostic phenotypes; however, late-onset depression appears to be less associated with family history of mood disorders and pre-morbid personality abnormalities and more associated with recent stressful events (Brodaty et al., 2001; Bukh, Bock, Vinberg, Gether, & Kessing, 2011; Burcusa & Iacono, 2007). This suggests that although the phenomenology of early and late-onset depression among older adults may be similar, they may result from different etiological factors. Investigations of these pathways have focused on age-related risk factors associated with structural and functional changes in the brain among older adults.

1.1.2 Vascular Depression

The vascular depression hypothesis was coined by Alexopoulos et al. (1997), following case observations of older adult patients suffering from depression. They proposed that cerebrovascular disease may predispose or exacerbate symptoms of depression via disruption of frontostriatal circuits responsible for emotion regulation and

executive function (discussed later). Evidence for the vascular depression hypothesis can be found in the high level of observed comorbidity between symptoms of depression and vascular disease. In one analysis, 53% and 42% of patients (*N* = 106, age range 19-82y) were diagnosed with major or minor depression 3 and 6 months respectively following an ischemic stroke (Kauhanen et al., 1999), which is the result of severe restriction or blockage of cerebral blood flow. Stroke may be one of the most acute vascular events associated with altered brain functioning, but evidence also suggests that more silent, but chronic conditions and markers of vascular disease may be associated with symptoms of depression in late life among those without history of stroke or major vascular event.

Magnetic resonance imaging (MRI) studies have allowed researchers to observe the associations of less severe, but none-the-less damaging small vessel diseases with depressive symptoms among older adults. Several MRI studies of depressed patients have shown greater volume of ischemic white matter lesions (shown as white matter hyperintensities, WMH) and lower neuronal density compared with age matched controls, particularly in the dorsolateral prefrontal cortex, orbitofrontal cortex, and in the caudate nucleus (Firbank, Llyod, Ferrier, & O'Brien, 2004; Khundakar, Morris, Oakley, & Thomas, 2011; W. D. Taylor et al., 2007; Thomas et al., 2002). Additionally, after adjustment for baseline depressive symptoms and cardiovascular risk factors, WMH volume, increases in subcortical infarcts, and decreases in brain volume have predicted depressive symptoms severity in 3-5 year prospective analyses among community dwelling older adults (Firbank et al., 2004; Godin et al., 2008; van Sloten et al., 2015). Although there is not yet a consensus on whether vascular depression represents a

distinct clinical subtype of depression (Sneed & Culang-Reinlieb, 2011), researchers are increasingly looking towards the possibility that various vascular risk factors may place some individuals at a higher risk for depressive symptoms later in life.

1.2 Vascular Risk Factors: Homocysteine and Apolipoprotein Genotype

The major vascular risk factors emphasized in this study are homocysteine and apolipoprotein genotype. In the sections that follow, the literature on each will be briefly discussed with regard to their vascular risk status and associations with cognitive performance and depressive symptoms.

1.2.1 Homocysteine

Homocysteine (Hcy) is a sulfur amino acid metabolite biosynthesized from ingested methionine found in many dietary proteins. Methionine, via its conversion to S-adenosyltransferase is essential in the stabilization of proteins including myelin and is also involved in the synthesis of melatonin, norepinephrine, and in the metabolism of serotonin. Normally, in concert with the folate (B9) cycle, Hcy is either converted back into methionine by cofactor cobalamin (B12) via re-methylation or converted to cysteine and taurine by pyriodoxine (B6) via trans-sulfuration (Ganguly & Alam, 2015; Refsum et al., 2004). Low dietary intake or absorption of B-vitamin cofactors are among the most common causes for elevated Hcy, defined as >15 µmol/L for adults aged 15-65 years of age (>12 µmol/L folic acid supplemented) and >20 µmol/L for adults >65 years of age (>16 µmol/L folic acid supplemented; Refsum et al., 2004). In addition to age, male gender, menopause, impaired renal function, and genetic factors (see section 1.2.2 for discussion of Apolipoprotein-E allele), several lifestyle factors have been associated

with high levels of Hcy including smoking, coffee and alcohol intake (Elias et al., 2008; Refsum et al., 2004).

1.2.1.1 Homocysteine and Cardiovascular Disease

Although some elevation of Hcy is typical in older age, high levels of Hcy through imbalances in production or elimination can cause oxidative stress, amyloid beta concentrations, plaque deposition, DNA strand breakage, and in turn apoptosis (Fuso et al., 2008). Additionally, high levels of Hcy can result in damage to endothelial cells and inflammation of blood vessels which can lead to atherogenesis and in turn cerebrovascular ischemia (Ganguly & Alam, 2015).

Despite the wellspring of recent research interest in Hcy, early evidence from case reports stretches back several decades. Observations from early archival case studies in the 1930's revealed an association between a genetically inherited inability to metabolize methionine, homocystinuria (high levels of urine homocysteine), and vascular insults among very young children and infants (Shih & Efron, 1970). Additional case studies in the 1950's and 1960's showed that in the most severe cases of homocystinuria, children experienced pronounced cognitive deficits, thromboembolic disease, and early death (Carmel & Jacobson, 2002). McCulley observed that despite having different enzymatic etiologies, many of these cases of homocystinuria also had advanced and widespread plaque buildup in major arteries resulting in arteriosclerosis (McCully, 2007). These observational studies were further supported by the experimental work of Mann et al. (1953), which showed that atherosclerosis and vascular lesions could be induced in Cebus monkeys with controlled variations of dietary sulfur amino acids.

Since these early clinical studies, large epidemiological studies have provided additional support for the link between cardiovascular disease and high levels of homocysteine. In a meta-analysis of 27 cross-sectional, case-control, and prospective studies, Boushey (1995) found that with every 5 μmol/L increase of total plasma homocysteine (tHcy) there was a 50% increase in cerebrovascular disease and estimated that 10% of coronary artery disease risk can be attributed to high tHcy. Additionally, Vollset et al. (2001) observed a dose-response relationship between higher levels of tHcy and all-cause mortality risk among adults 40-67 years of age (average follow-up 4.1 years), particularly among individuals with high risk for cardiovascular disease (CVD).

These findings have been further supported by experimental epidemiology analysis. A United States and Canadian population study observing the effect of folic acid fortification of enriched grain products from 1998-2002 showed increases in average blood folate concentrations, reductions in plasma total homocysteine (tHcy), and significant incremental decreases in stroke mortality compared with the pre-enrichment period (1990-1997), even with adjustment for societal level changes in known cardiovascular risk factors such as cigarette smoking, hypertension, diabetes, and high total serum cholesterol (concentration ≥240 mg/dl). Interestingly, this prevalence rate decline was not found in England and Wales where folate fortification was not required (Yang et al., 2006).

1.2.1.2 Homocysteine and Depressive Symptoms

Among other well-recognized cardiovascular risk factors, high levels of Hcy have also been a target of interest in the development of affective disorders, particularly in

later life. Much of the research on Hcy and depressive symptoms has been cross-sectional. Almeida et al. (2008) conducted a meta-analysis of 9 observational studies mainly consisting of older community-dwelling adults (*N* = 7,114) as well as data from the Health in Men Study (*N* = 4,245). Of the 9 total studies included for analysis, 6 showed positive associations between tHcy and clinically significant levels of depressive symptoms (i.e., > survey cut score thresholds) or diagnosed major/minor depression (Almeida et al., 2005, 2008; Bjelland et al., 2003; Bottiglieri et al., 2000; Cassidy et al., 2004; Tolmunen et al., 2004). In all, Almeida et al. estimated that those with high levels of tHcy were 70% (95% CI: 1.38-2.08) more likely to have clinically significant levels of depressive symptoms compared those with lower levels of tHcy after adjusting for a range of medical comorbidities and cardiovascular risk factors. However, two cross-sectional studies in this analysis failed to find an association between high levels of tHcy and clinically significant levels of depressive symptoms. Penninx et al. (2000) failed to find any association in a sample of disabled women (>=65y) and Tiemeier et al. (2002) did find an initial association between depression status and high tHcy, but this association was non-significant when adjusting for cardiovascular disease. Although these cross-sectional results are promising, longitudinal research is necessary to determine whether Hcy contributes as a potential risk factor for depressive symptoms over time rather than just being associated with depressive symptomatology.

Few prospective studies have been conducted, but results have been generally supportive of higher baseline tHcy predicting clinically significant levels of depressive symptoms at 4-year follow-up in women (Forti et al., 2010) and in men (combined baseline/followup risk; Tolmunen et al., 2004). In one Korean sample, which excluded

baseline depression and adjusted for age, gender, education, Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh PR, 1975), disability, smoking, problem drinking, physical activity, and vascular risk, decreases in B12/B9 and increases in tHcy over a follow-up period of 2.4 years all predicted increased depression incidence (Kim et al., 2008).

1.2.2 Apolipoprotein-E4 Genotype

Genetic factors relating to vascular function may moderate the relationship between tHcy and vascular depression. The apolipoprotein (APOE) gene provides information necessary for the synthesis of the APOE-E protein. This protein binds to lipids creating lipoproteins, which are responsible for packaging and carrying cholesterol and other fats through the blood stream. Carriers of at least one APOE-E4 allele have been shown to have significantly higher rates of CVD and cognitive impairment/dementia (Eichner, 2002; Small, Rosnick, Fratiglioni, & Backman, 2004) and previous cross-sectional studies from the Maine-Syracuse Longitudinal Study (MSLS) have shown that carrying at least one APOE-E4 allele may multiply the risk associated with higher tHcy for lower cognitive performance (Elias et al., 2008).

Although cross-sectional evidence for the association between depression and the APOE-E4 allele has been mixed, most of the studies conducted thus far have included small sample sizes, which may lack sufficient statistical power for detecting group differences in complex regression models (Evans & Rajan, 2015). Additionally, a recent 5 and 9-year prospective study of older adults has shown positive associations between the APOE-E4 allele, depressive symptoms, and late life minor depression incidence (Skoog et al., 2015). Another 1-year prospective study found no difference

between depressed and non-depressed older adults with regard to cognitive decline, but significant differences in decline when comparing depressed and non-depressed individuals carrying the APOE-E4 allele (Niti, Yap, Kua, & Ng, 2009). It is unclear if the APOE-E4 allele affects the directional association between executive function and depressive symptoms, but it is possible that failing to account for APOE genotype may explain previously negative findings in studies using relatively invariant outcome measures (i.e., depression diagnosis, MMSE).

1.3 Cognitive Performance

Like depression, cognitive performance can be considered a unitary construct or one made of up several associated factors. Cognitive performance in this context can also be measured as a categorical-clinical construct or as a continuum of ability ranging from low to high. Dementia is the most severe level of cognitive deficit with mild cognitive impairment (MCI) being considered an intermediate stage of decline from normal functioning (Petersen et al., 2001). Broadly defined, MCI is cognitive decline which is greater than would be expected for an individual's age or education level (often at least 1.5 standard deviations), but does not interfere with one's ability to live independently as is seen in the case of dementia (Abner et al., 2012). The decision to diagnose dementia (National Institute of Health, 2013) or MCI is often based on professional agreement derived from patient/ caregiver interview and cognitive testing. Importantly, these are clinical definitions of severity rather than etiology of cognitive decline, which is quite heterogeneous. The most common conditions associated with dementia are Alzheimer's disease (AD) followed by, Vascular Dementia (VaD), Frontotemporal Dementia (FTD), Synucleinopathies, and Huntington's Disease

(National Institute of Health, 2013). Although cognitive performance is often considered a continuous construct, MCI and dementia as clinical constructs can provide caregivers and researchers with a common language to understand the scope of the problem of cognitive decline among older adults.

1.3.1 Prevalence and Course of Cognitive Impairment

There are upwards of 24.3 million adults living with dementia world-wide and the number of individuals with dementia is expected to rise to 81.1 million by 2040 (Ferri et al., 2005). The average age of the U.S. population continues to rise as individuals are able to live longer and as such so does the burden of cognitive impairment (Ortman, Velkoff, & Hogan, 2014). Currently 3-21% of individuals over the age of 65 in the U.S. are estimated to have MCI and roughly half of these individuals go on to develop dementia within five years of initial diagnosis (Gauthier et al., 2006; Manly et al., 2008; Petersen et al., 2001).

Aging and the transition from normal functioning to MCI may impact several cognitive domains, but some aspects of cognitive functioning are more likely to be impacted by the aging process. Evidence is broadly consistent with Cattell and Horn's (1967) crystalized-fluid model of aging. Older adults tend to experience the greatest declines in domains associated with novel problem solving (i.e., executive function, working memory, processing speed, and perceptual reasoning) compared with performance associated with total fund of knowledge and overlearned skills (Glisky, 2007; Harada et al., 2013). While significant declines in any cognitive domain may be problematic, recent research has highlighted the particularly important role of executive function in maintaining functional independence.

1.3.2 Cognitive Impairment and Executive Function

Although researchers vigorously debate how to operationalize the construct of executive function, a general consensus on its definition has existed since its first introduction in Baddeley and Hitch's model of working memory (1974). Broadly speaking, executive function is a set of high-order mental processes that involve response inhibition, working memory, and mental flexibility (Alvarez & Emory, 2006; Diamond, 2014). These core executive functions form the basis for planning and decision-making, troubleshooting and adapting to novel situations, and effortful inhibition of habitual behaviors (Jurado & Rosselli, 2007). Significant deficits in executive function have been observed among older adults with MCI across clinical subtypes (amnesic vs. non-amnesic and single vs. multiple domain; (Brandt et al., 2009; Traykov et al., 2007; Zheng et al., 2012). Additionally, these declines may precede disturbances in global functioning and memory and measures associated with executive function have been shown to have incremental utility in predicting transition from normal functioning to MCI/dementia (Carlson, Xue, Zhou, & Fried, 2009; Elias et al., 2000; J. K. Johnson, Lui, & Yaffe, 2007; Ratcliff, Dodge, Birzescu, & Ganguli, 2003).

1.3.3 Cognitive Performance and Vascular Disease

The associations between cardiovascular disease and cognitive performance in middle and later adulthood has been well established through a series of carefully conducted observational studies following participants over the entire adult lifespan (Elias, Goodell, & Dore, 2012; Framingham Heart Study, 2016). Much like depression, individuals who have experienced acute vascular attacks such as stroke are at an increased risk for cognitive impairment following the event. There is a considerable

number of variables which affect the likelihood for cognitive impairment post-stroke, but prevalence estimates range from 20 – 80% depending on age, race, and diagnostic criteria being applied (Sun, Tan, & Yu, 2014). These strong associations led to the recognition of vascular cognitive impairment/dementia, which has been expanded to include impairment in the presence of more silent cerebral small vessel conditions such as WMH and lacunar infarcts (Brickman et al., 2009; Vermeer et al., 2009). Other studies have found consistent positive associations between total cardiovascular risk factor load and poorer cognitive performance for visual-spatial memory, working memory, processing speed, executive function, and global performance more generally (Crichton, Elias, Davey, & Alkerwi, 2014; Reis et al., 2013; Sabia et al., 2009).

1.3.4 Cognitive Performance and Homocysteine

As a well-recognized cardiovascular risk factor, interest in the association between Hcy, vascular disease, and cognitive performance has increased exponentially since the mid-1960's (Robinson, 2000). In cross-sectional analyses, tHcy level has been observed to be inversely associated across multiple domains of cognitive performance (Elias et al., 2005, 2006), and perhaps most strongly with processing speed and executive function (Polito et al., 2016; West et al., 2011). Additionally, in 3 and 8-year prospective analysis, high baseline tHcy was found to be predictive of conversion from normal cognitive functioning to MCI and dementia (Gabryelewicz et al., 2007; Seshadri et al., 2009). Importantly, many of these findings were adjusted for a range of demographic factors, comorbid cardiovascular disease, and psychiatric illness. Individuals with vascular cognitive impairment also tend to have higher tHcy and lower B12 and folate compared with either stroke patients without cognitive impairment or

healthy controls, indicating an incremental cognitive risk with increasing levels of tHcy (Jiang et al., 2014). For an extended literature review on homocysteine, vitamins, and cognitive functioning see Crichton, Robbins, and Elias (2015).

Not all individuals experience similar lowering in cognitive functioning as a result of high tHcy. There appears to be cross-sectional evidence for an interaction between age and high tHcy. Specifically, the relationship between high tHcy and poor cognitive function appears to be strongest among older adults (Agrawal et al., 2015; Elias et al., 2005). Although many cardiovascular disease risk factors were statistically controlled in these studies, Agrawal et al. (2015) speculate that high levels of Hcy are more likely to co-occur in the presence of other aging related markers of vascular disease, which may have a synergistic impact on cognitive decline.

1.4 Executive Function, Aging, and Symptoms of Depression

One possible mediator for the relationship between vascular risk factors such as tHcy and depressive symptoms may be through deficits in cognitive performance and more specifically deficits in executive function through vascular insult. In the next sections, we discuss profiles of depression-executive dysfunction among older adults, followed by a review of the literature on the directional associations of cognitive performance and depressive symptoms and possible mechanisms of decline.

1.4.1 Depression-Executive Dysfunction Syndrome

There is consistent evidence that individuals experiencing the acute phase of depression have lowered cognitive performance across multiple domains and ages (i.e., executive function, attention, memory, processing speed; Hammar & Ardal, 2009).

Bipolar patients with high levels of tHcy tend to perform worse on the Verbal Comprehension and Perceptual Organization subtests of the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981) and on the Stroop task, particularly among men (Permoda-Osip, Kisielewski, Dorszewska, & Rybakowski, 2014). However, although depressed younger adults experience a range of deficits compared with non-depressed peers, older depressed adults with poor vascular risk profiles and both young and older adults who have experienced an ischemic stroke experience significantly greater deficits in executive function, processing speed and gait slowing/impairment compared with their non-depressed peers (Hajjar et al., 2009; Lockwood, Alexopoulos, & van Gorp, 2002; Sanders, Bremmer, Comijs, Deeg, & Beekman, 2016; Sobreiro et al., 2014), indicating possible interactions between aging, vascular disease, and depression.

1.4.2 Directional Associations of Executive Function and Depressive Symptoms

It is important to determine the directionality between depressive symptoms and cognitive impairment because this may provide caretakers and clinicians with information for predicting disease trajectory. There is a small, but burgeoning literature on the predictive value of low executive function and disruptions in frontostriatal pathways and poor antidepressant treatment response among older adults, (Sheline et al., 2010; Sneed et al., 2007; Tam & Lam, 2013). Additionally, if executive functioning is predictive of future depressive symptoms, tests of executive functioning may be considered for predicting risk of future episodes following treatment (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002). Even small reductions in the development or severity of cognitive impairment or depressive symptoms through early detection,

treatment, and monitoring could have considerable positive impacts at the population level (Fiske et al., 2009; Zhu et al., 2013).

So far, only a few studies have systematically reviewed the reciprocal relationship between depressive symptoms and cognitive functioning. One study among older Hispanic adults (*N* = 194, Mean age = 78.5) examined this relationship over a 3-year period using a structural equation modeling technique known as cross-lagged panel analysis. In this study, the researchers measured global performance with 3 subtests (California Verbal Learning Test, Color Trails Test, Part 2, Fuld Object Memory Evaluation) to represent short-term verbal learning, tracking, and short-term object memory. They found that cognitive performance predicted subsequent depressive symptoms (CES-D), but that depressive symptoms did not predict subsequent cognitive performance when controlling for age, gender, and financial strain (Perrino, Mason, Brown, Spokane, & Szapocznik, 2008). Given that this analysis was restricted to advanced-aged adults; it remains unclear if these findings can be generalized beyond later-life cognitive decline. In addition, this study did not specifically analyze executive function outcomes (aside from inclusion in the composite) or adjustment for vascular risk factors which may underlie the association between cognitive performance and depressive symptoms in later life.

In another 2-year cross-lagged panel design of older adult (=> 65) primary care patients (*N* = 284), Cui, Lyness, Tu, King, and Caine (2007) found the opposite results. Depression diagnosis predicted subsequent executive function performance (Trails B and Trails B-A), but executive function did not predict depression diagnosis. Sensitivity analysis revealed similar results when including both subjects with dementia and those

with a history of non-late onset depression. Additionally, they rescored the Hamilton Depression Rating Scale (Hedlund & Viewig, 1979) to exclude vegetative symptoms assumed to be epiphenomena of vascular depression (i.e., decreased activities/ libido, gastrointestinal symptoms, weight loss, insomnia, psychomotor retardation, agitation, diurnal variation, and other somatic symptoms) and found similar results, indicating a more general longitudinal relationship between depression and executive function, particularly in set shifting and response inhibition. Major strengths of this study were the inclusion of adjustments for chronic illness and vascular disease and the measurement of executive function outcomes. However, Cui et al. failed to account for error covariance at baseline between depression and executive functioning, so it is unclear if depression diagnosis actually predicted lowered executive functioning, or if depression was just a concurrent risk in the presence of low executive function, and continued risk for poor executive function 2-years later. Additionally, attrition (approx. 60%) was considerably high, with non-completers more likely to have low scores on the initiation/perseveration subscale of the Mattis Dementia Rating Scale. This likely reduced the ability of Cui et al. to detect variation in depressive symptoms over time as a result of cognitive dysfunction. Moreover, Cui et al. used multinomial logit regression for predicting depression diagnosis (i.e., major, minor, none) which may have further reduced their ability to detect subtle changes in depressive symptoms in comparison to the use of continuous depressive symptom scores.

Lastly, a 2-year analysis of Korean community members (Yoon, 2014; Age > 65, *N* = 3,511), revealed that both cognitive performance (measured by Korean-Mini Mental State Exam) and depressive symptoms (CES-D Korean version) were negatively

associated in lagged analysis, indicating a possible reciprocal relationship. The significant bidirectional results of Yoon's analysis may be a reflection of adequate sample size to detect both causal pathways; however, their observed associations were also modest. Additionally, Yoon did not include any adjustment for cardiovascular disease. While the MMSE is an adequate screening measure for dementia, it is not designed to detect subtle variations in executive function, which may be early indicators for depression and cognitive impairment compared with recall (Juby, Tench, & Baker, 2002).

To our knowledge there has been no study to date that has systematically explored these relationships over longer periods of time and across a wide range of age groups. This is a particularly salient issue given the long latency period for cognitive impairment and the potential benefits for early prediction of risks to independent living. It is possible that the longitudinal relationship between executive function and depressive symptoms change over the lifespan, becoming more strongly associated in older adulthood in the presence of greater allostatic load and vascular impairment (Lockwood et al., 2002). Additionally, no study to date has explored the mediating role of executive function between tHcy and depressive symptoms.

1.4.3 Possible Mechanisms of Decline

It is possible that prolonged exposure to high tHcy results in cerebral hypoperfusion and WMH which impairs executive functioning. Both loss of perceived (Lawrence, Roy, Harikrishnan, Yu, & Dabbous, 2013) and actual cognitive ability could explain the link between low executive function and future risk for depressive symptoms among older adults. In general, depressed individuals tend to generate fewer and less

appropriate problem-solving strategies under cognitive load (Channon & Green, 1999). Poor executive function has also been associated with avoidant coping strategies among stroke survivors (Kegel, Dux, & Macko, 2014) which may increase the risk for future depressive episodes.

It is also plausible that depression is an independent risk factor for high tHcy and subsequent executive dysfunction. Among women 20-34 years of age (*N* = 5,051) depressive symptoms predicted both concurrent and subsequent lower folate levels over a two year period. However, folate did not predict future depression (Kendrick et al., 2008). Stressful life events may increase the risk for symptoms of depression such as lower physical activity and dietary disturbance which may increase risk for high tHcy (Okura et al., 2006; Rahman et al., 2013), poor vascular functioning, and subsequent executive dysfunction. Additionally, several longitudinal analyses reviewed by Hammar and Ardal (2009) concluded that executive function and processing speed dysfunctions are not limited to depressive episodes. These impairments tend to persist during symptom remission, reflecting a possible cognitive scarring effect of depression (Burcusa & Iacono, 2007; Gorwood, Richard-Devantoy, Baylé, & Cléry-Melun, 2014). However, none of these analyses accounted for cognitive performance prior to experiencing a depressive episode, so it is yet unclear whether depressive episodes represent a true risk for executive decline or if poorer executive functioning is simply a characteristic of those more likely to experience depressive episodes and is relatively invariant with regard to changes in clinical categorization. Lastly, it is possible that tHcy represents a secondary marker for cerebral vascular disease rather than an independent cause (Wierzbicki, 2007) and variations in cognitive function and

depressive symptoms may be explained by already well-established vascular risk factors.

1.5 Study Hypotheses in Relation to Objectives

No studies to our knowledge have: 1) analyzed the bidirectional associations of depressive symptoms and executive function in the context of a full range of other cognitive domains; or 2) investigated the extent to which age and APOE-E4 genotype moderate the prospective associations of homocysteine and depressive symptoms and the extent to which executive function mediates the prospective associations of homocysteine and depressive symptoms.

Objectives of the proposed work with respective hypotheses were as follows:

1. To examine the cross-sectional (at wave 6) associations of executive function and depressive symptoms.

Hypothesis: Executive function will be associated with depressive symptoms at wave 6.

2. To examine the cross-lagged prospective associations (wave 6 to wave 7) of executive function with depressive symptoms.

Hypothesis: The strength of associations of wave 6 executive function and wave 7 depressive symptoms (adjusted for wave 6 depressive symptoms) will be stronger compared with the strength of associations of wave 6 depressive symptoms and wave 7 executive function (adjusted for wave 6 cognitive function).

3. To determine whether age and APOE-E4 genotype (wave 6) moderate the prospective associations of homocysteine (wave 6) and depressive symptoms (wave 7, adjusted for wave 6 symptoms).

Hypothesis: APOE-E4 genotype and age will moderate the associations of wave 6 homocysteine and wave 7 depressive symptoms. Specifically, among those with higher homocysteine, older adults who are APOE-E4 carriers will experience the greatest increases in depressive symptoms.

4. To determine the extent to which executive function mediates the associations of the age x APOE-E4 x homocysteine interaction (wave 6) and depressive symptoms (wave 7, adjusted for wave 6 symptoms).

Hypothesis: Wave 6 executive function will mediate the conditional association of the age x APOE-E4 x homocysteine interaction (wave 6) and depressive symptoms (wave 7, adjusted for wave 6 symptoms), such that significant indirect conditional paths will be observed for this interaction on increases in depressive symptoms through executive function.

5. To determine the specificity of the associations between executive function, depressive symptoms, and the above CVD-RF's in the context of a full range of cognitive domains.

Hypothesis: The associations of executive function, depressive symptoms, and the above CVD-RF's will be similar across a broad range of cognitive domains.

2. METHODS

2.1 The Maine-Syracuse Longitudinal Study Design

Since its inception in 1974, the Maine Syracuse Longitudinal Study (MSLS) has studied the relationships between cardiovascular health and cognitive functioning for over three decades. The original studies were primarily concerned with the effects of idiopathic and uncomplicated hypertension on cognitive functioning and have since expanded dramatically to include several other cardiovascular risk factors such as tHcy, arterial stiffness, diabetes, cholesterol, kidney function, physical activity and performance, and nutrition. Along with these measures, several other measures of psychosocial functioning such as symptoms of depression, anxiety, and social activity were assessed, most often for consideration as covariates in cognitive models. The MSLS includes seven waves of examination with six participant cohorts defined by time of entry into the study. A total of 2464 community-dwelling individuals have participated in at least one examination of the MSLS (see Table 2.1).

The first four waves of the MSLS were conducted at the SUNY Health Science Center in Syracuse, New York via collaboration between Merrill F. Elias, Principal Investigator and David H. P. Streeten, Investigator and Professor of Medicine. In 1996, the MSLS acquired its own laboratory space in Syracuse while collaborating with medical staff at the SUNY Health Sciences Center. This study structure continued through wave 6 and wave 7.

Table 2.1. 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

W – Wave C – Cohort E – Examination

2.2 Sample and Design

Data were selected from the sixth [2001-2006] and seventh [2006-2011] waves of the MSLS from non-institutionalized community-dwelling adults residing in Central New York. Exclusions of MSLS participants were done on a study by study basis based on medical, and social psychological, demographic information obtained during their MSLS participation, including hospital and patient record (by permission). Exclusions for the current study are described later. The University of Maine Institutional Review Board approved this study (reference number: 2005-07-04) and informed consent was obtained from all participants.

For this study participants were excluded for the following: probable dementia (*n* = 8), kidney dialysis (*n* = 5), and acute stroke (*n* = 28) at wave 6 or wave 7. Additionally, 196 individuals were not invited back for participation in wave 7 due to living outside of the Central New York area and the necessity that participants visit the MSLS laboratory for assessment of pulse wave analysis and pulse wave velocity. Of the 822 individuals eligible for study, 103 did not return for wave 7 for other reasons (87.5% retention). Although we did not exclude those with mild cognitive impairment or a history of depression treatment in order to obtain a wide range of continuously distributed data for cognitive performance and depressive symptoms, we excluded individuals with probable dementia (*n* = 8) as they were unable to complete much of the MSLS cognitive test battery. Acute stroke (*n* = 28) and kidney dialysis (*n* = 5) are highly related to both cognitive dysfunction and symptoms of depression and those with a history of acute stroke were excluded due to their likely confounding effects (Elias et al., 2009; Kauhanen et al., 1999; Sobreiro et al., 2014) on these outcomes.

Acute stroke is defined as suffering a focal neurological deficit of acute onset lasting greater than 24-hours as determine by medical record review. A diagnosis of probable dementia was based on MSLS cognitive battery performance, medical record review, significant other interview, and consensus derived from expert committee review (neuropsychologists, social psychologists, and a geriatric physician) based on National Institute of Neurological Disorders and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders (NINDS-ADRDA; Mckhann et al., 2011) criteria.

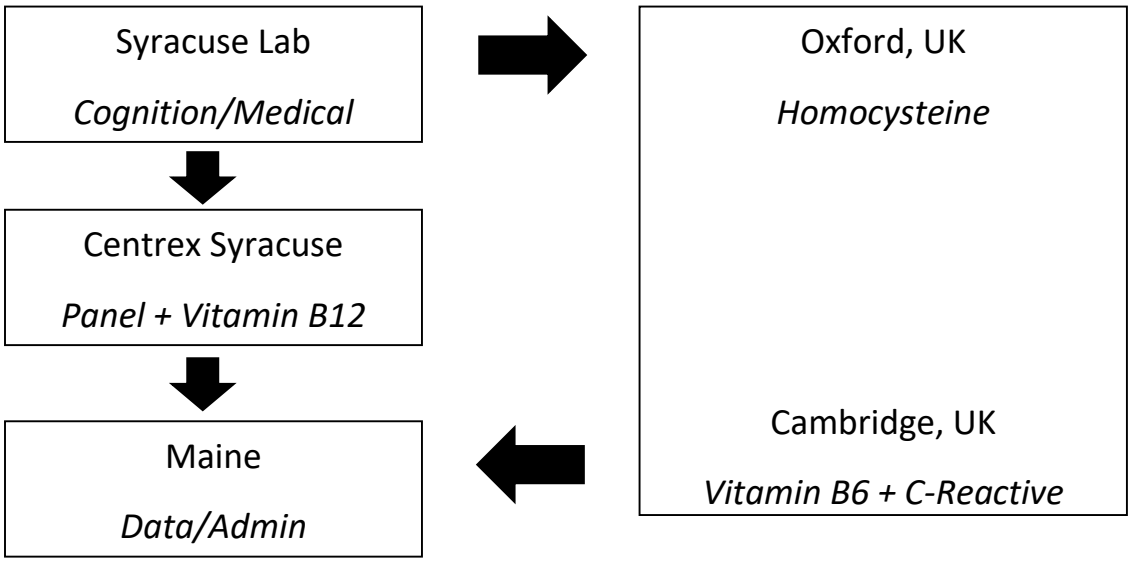
2.3 Procedure

For waves 6 and 7 paper and pencil questionnaires including demographic data, job stress, sleep disturbance, Cornell Medical Index, general medical information, and health habits (smoking, alcohol consumption, dietary data, etc.) were completed at home within one week of arriving at the MSLS laboratory. Participants arrived at the laboratory around 9:00 AM following a fasting period maintained since 12:00 AM unless they were diagnosed with diabetes mellitus and physician approval was not obtained. Once in the laboratory, participants provided additional medical interview information on physical and mental health. Blood samples were then taken first when the participant arrived followed by fifteen blood pressure measurements (5 each: sitting, standing, and recumbent; GE DINAMAP 100DPC-120XEN; GE Healthcare), and pulse wave analysis (wave 7).

Wave 6 and wave 7 assay collection methods for independent variables including tHcy have been described in greater detail in (Elias et al., 2006). Plasma samples for tHcy and B6 were stored at -40°C and shipped to Oxford and Cambridge, UK for assessment. Samples for assays of cholesterol, creatinine, plasma B9/B12, and glucose were stored on ice and sent to Centrex Clinical Laboratories, Syracuse, New York. tHcy sample concentrations were analyzed using a fluorescence polarization immunoassay (Axis-Shield, Dundee, UK) on an Abbott IMx auto-analyzer (Abbott Laboratories, Chicago, IL, USA; Shipchandler & Moore, 1995). The average intra-assay variation was within accepted norms reported by the Centers for Disease Control (< 3.5%, CDC, 2015). Additional details regarding assay collection have been described in Elias et al. (2006).

In addition to the assays above, APOE genotype (collected at wave 6 or wave 7) was defined as those with at least one APOE-E4 allele vs. other (4/4 genotype: 2.8%; 2/4, 3/4, and 4/4 combined genotypes: 22.8%). APOE genotyping was derived from polymerase chain reaction and restriction enzyme digest with Hhal (Hixon & Vernier, 1990) at the Neuroscience Division, Medical School, University of Birmingham, UK. Following assay collection, participants were provided with a light breakfast and then given a physical examination and were interviewed regarding medical history, medications, and current treatment. Figure 2.1 displays the different locations involved in MSLS data collection as well as where specific assays were done.

Figure 2.1 MSLS Structure and Assessment Locations



Following interview, participants completed the MSLS Neuropsychological Battery of over twenty order-standardized tests from the Wechsler Memory Scale-Revised (WMS-R), the Wechsler Adult Intelligence Scale (WAIS and WAIS-III), MMSE, and Boston Naming Test among several other assessments. All cognitive measures

were completed in a uniform order to preserve the standardized subtest presentation within each scale and participants were allowed breaks as needed between subtests. Following the examination, participants were sent a summary of their medical and cognitive examination with a request that they contact their personal care provider to review the information.

Age and education were operationalized in number of years attained, sex (M/F) and marital status (married or living with partner/ divorced, separated, single, or widowed) were dichotomized as was ethnicity (Black/ Other) due to the low number of non-Black minority participants (Black: 6.1%, Native American: 1.0%, Hispanic: 0.4%, Asian: 0.1%) and to ensure consistency of coding with prior MSLS studies. Body Mass Index (BMI) and obesity status (yes/no) were derived from objective measurement of height and weight without heavy clothing. Self-reported number of close friendships, social activity (Robbins et al., 1994), and recent life events (yes/no), and co-residency (yes/no) were also evaluated for use as covariates.

The Zung Depression Inventory (ZDI; Zung, 1965) was used to measure symptoms of depression at every wave of the MSLS. The ZDI is composed of 20 self-reported, Likert scale items ranging in frequency from 1 “a little of the time” to 4 “most of the time” and summed to create a total raw score (see appendix A for item list). Raw scores were then divided by 0.8, resulting in an index score range from 25 to 100 (Hunter & Murphy, 2011). At both wave 6 and wave 7, ZDI items showed good internal consistency ($\alpha = .80$). Index scores were used to represent the continuum of depressive symptom severity rather than major depressive disorder incidence. For a more thorough review on dimensional scale measurement and the associations

between the ZDI and other depression scales see Crawford, Cayley, Lovibond, Wilson, & Hartley (2011).

In order to aggregate the effect of an array of cardiovascular risk factors, the Framingham CVD Risk Score, which has been shown to predict 10-year risk of cardiovascular disease, was employed (D'Agostino et al., 2008). The Framingham CVD Risk Score includes age and gender stratified weights based on assay results of total cholesterol (TC), high density lipoprotein (HDL), smoking status (self-report), and systolic blood pressure (measurement explained above) stratified by treatment status in addition to diabetes mellitus diagnosis status (see item weights in Appendix B). Estimated glomular filtration rate was determined from serum creatinine (two-point rate test type utilizing Johnson and Johnson VITROS instrument; Ortho Clinical Diagnostics) stratified by age, sex, and ethnicity (Levey, Bosch, & Lewis, 1999). Diabetes mellitus was defined as those with a fasting glucose level of ≥ 126mg/dl (assay methods described in Elias et al., 2006) or treatment for diabetes mellitus.

2.4 Cognitive Tests and Domains

Cognitive performance was originally assessed using the Wechsler Adult Intelligence Scale (WAIS) and the Halstead-Reitan Neuropsychological Test Battery. In 1993, the Framingham Test Battery was included and specific tests were selected from these and other measures were selected to be included in the Maine Syracuse Longitudinal Study Test Battery at wave 6 in 2000. Subtests and scales included in the battery were measured on continuous scales and used to create measures of several cognitive domains/composites shown in Table 2.2.

Principal components and factor analyses by Elias et al. (2006)., yielded four broad cognitive domains within a Global composite (i.e., Visual-Spatial Memory and Organization (VSOM), Verbal Episodic Memory, Scanning and Tracking, and Working Memory) derived from the Z-transformed average of 17 different subtests. Additionally, the WAIS Similarities subtest has been employed as a separate measure in the MSLS because it loaded significantly across the above cognitive domains. In some later studies an Executive Function composite was created (discussed below). For descriptive purposes for this study and prior MSLS analyses, subtests were Z-transformed, summed with their respective composite subtests, and z-transformed again to create standardized composite scores. Each composite score had a mean of 0.00 with a standard deviation of 1.00. Similarly, the Global composite was created by taking the z-transformed average of all the individual subtests used in each composite, consistent with established MSLS practice. For all models below, we analyzed cognitive performance data for the Global composite, Visual-Spatial Memory and Organization (VSOM), Verbal Episodic Memory, Scanning and Tracking, Working Memory, as well as an expanded version of the Executive Function composite employed in prior MSLS studies.

Table 2.2 Descriptions of the Cognitive Tests Contributing to Each Composite Score

Composites/ Subtests	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 and construction
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 functioning
Similarities [a]	Abstract reasoning
Executive Function	
Trail Making B [d]	Trails A plus demands on executive function abilities
Controlled Oral Word Associations	Verbal fluency and executive functioning
Expanded Executive Function (current study)	
Trail Making B – A	Executive function/set shifting with Trails A scanning/tracking removed
Controlled Oral Word Associations	Verbal fluency and executive functioning
Block Design [c]	Visual-spatial perception, organization and construction
Matrix Reasoning [b]	Abstract reasoning and pattern recognition

[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

2.4.1 Expanded Executive Function Measure

For this particular study, an expanded version of the original MSLS Executive Function composite (i.e., Controlled Oral Word Associations and Trail Making Test B-A) was developed. Two additional subtests (i.e,, Block Design and Matrix Reasoning) were included in order to broaden the range of executive abilities assessed and to increase reliability of the Executive Function construct. Subtests were included for study based on their theoretical relevance to different aspects of Executive Function (EF) and on their incremental improvement to scale reliability (wave 6 α = .77; wave 7 α = .78). The Clock Drawing Test was considered for inclusion because of its widespread use as a measure of Executive Function and planning (Juby, Tench, & Baker, 2002), but it was ultimately dropped due to a lack of performance variability (i.e., ceiling effect) for our sample.

The importance of the Executive Function measure for this study warrants a detailed description of each of the component tests, Block Design, Matrix Reasoning, Controlled Oral Word Association, and Trail-Making.

For the Block Design subtest (BD; Wechsler, 2003), participants were given blocks which had red, white, and half red/half white sides. Participants were then asked to use the blocks to match a visual pattern presented by the examiner as quickly as possible. Time-to-completion and accuracy both factor into the scoring of BD performance. Participants were presented with novel patterns which became increasingly difficult until the participant consistently did not complete the pattern within the allotted time, failed to correctly reproduce the pattern, or the participant completed all patterns available, at which point the subtest was concluded. BD has been shown in

other studies to be sensitive to variations in central executive function (updating), prefrontal lobe damage, and age-related decline (Brown, Brockmole, Gow, & Deary, 2012; Friedman et al., 2006; Lezak, 2012).

For Matrix Reasoning (MR; Wechsler, 2003), participants were presented with an incomplete pattern matrix and a set of five individual patterns from which to select to complete the matrix pattern. Individual patterns are selected based on concepts such as numbers and types of shapes, orientation, and color. Like BD, novel pattern matrices were presented in standard order of increasing difficultly and participants continued until all levels had been completed or when they consistently failed to choose the correct pattern. Participant scores were determined by number of correctly completed matrices. MR was selected as an alternative index of fluid reasoning because unlike BD, participants were given as much time as needed to make their selection, reducing the overall reliance on speeded processing.

For Controlled Oral Word Associations (COWA; Benton, 1967; Patterson, 2011), participants were given one minute to verbally list as many words beginning with the same letter (i.e., F) as possible. Two additional rounds were completed with different letters (i.e., A, S). Participants were also asked not to repeat words, list proper nouns, numbers, or repeat words with different suffixes (e.g., fence and fences). Participant scores were determined by number of correctly listed words. COWA has been shown to correlate moderately with other measures of executive function, including the Wisconsin Card Sorting Task and Trail-Making Test – B and to be sensitive to performance variability following antidepressant treatment for stroke patients and those

with frontal lobe lesions (Duff, Schoenberg, Scott, & Adams, 2005; Levin, Eisenberg, & Benton, 1991; Narushima, Paradiso, Moser, Jorge, & Robinson, 2007).

For The Trail-Making Test (Jurado & Rosselli, 2007; Reitan, 1958), participants were given a sheet of paper which had circles distributed throughout. In Part A, participants were asked to draw a trail to connect the circles in ascending order as quickly as possible (circles were numbered 1-25). In Part B participants were given another sheet of paper, only the circles included both numbers (1-13) and letters (A-L). Participants were then asked to draw a trail to connect the circles in ascending order alternating between numbers and letters (i.e., 1-A-2-B-3-C) as quickly as possible. Time taken to complete the tasks was recorded in seconds, with less time representing greater performance. The log-transformed difference in seconds between Part B and Part A (TMT B-A) was calculated to minimize the effect of processing speed and to better isolate demand on set shifting and response inhibition represented by Part B (Cui et al., 2007; Jurado & Rosselli, 2007).

2.5 Statistical Methods

Statistical analyses initially consisted of selecting theoretically relevant covariates, analyzing bivariate associations between covariates, the Executive Function composite and symptoms of depression. Lastly, analysis of path models was conducted with basic and extended sets of covariates.

2.5.1 Covariate Selection

Previous studies have identified several theoretically relevant covariates with respect to Executive Function, tHcy, and symptoms of depression (see Appendix C).

After identifying commonly occurring covariates in the literature, covariates were eliminated initially based on a lack of association with any of the following: Executive Function, tHcy, or symptoms of depression ($p > .10$).

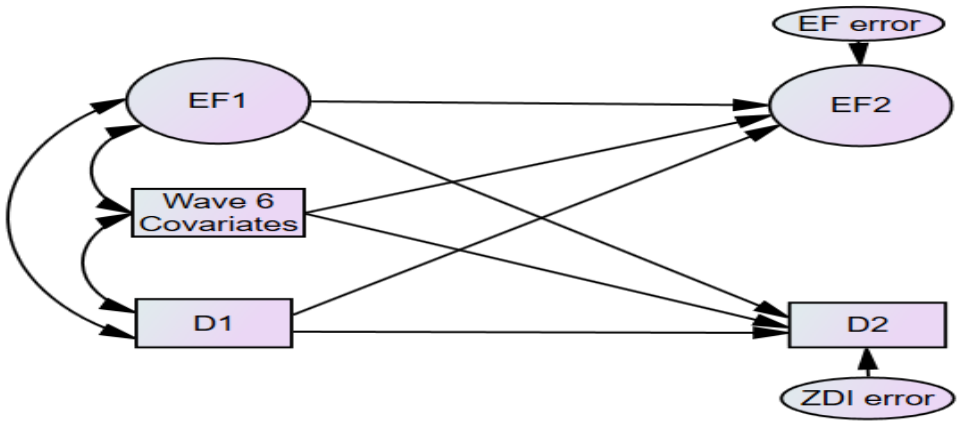
A basic covariate set was employed in all analyses (age, sex, education, ethnicity, and marital status) and other covariates were included based on their contributions to model fit as represented by reductions in the $\chi 2$ statistic. However, since the $\chi 2$ statistic is almost always significant ($p < .05$) with large sample sizes ($n > 400$; Kenny, 2015), other measures were employed which are not as prone to type-one error ($\chi 2/df$, root mean squared error of approximation (RMSEA), and comparative fit index (CFI). Although many of these variables did not have a considerable negative impact on model fit statistics, diminishing returns on model fit were observed. Once model fit indices were observed to be satisfactory, several covariates were excluded in order to achieve model parsimony.

2.5.2 Cross-Lagged Panel Design

We utilized a structural equation modeling technique known as cross-lagged panel design (CLPD, SPSS V.24 AMOS). In this study, wave 6 Executive Function (EF1) and depressive symptoms (D1) and wave 7 Executive Function (EF2) and depressive symptoms (D2) are the variables of interest. A simplified version of the CLPD employed in this study is displayed in Figure 2.2 below. This CLPD produces 6 possible associations, 2 synchronous (cross-sectional; D1-EF1, D2- EF2), 2 auto-correlational (D1-D2, EF1-EF2) and 2 cross-lagged (EF1-D2, D1-EF2). This design allows the 2 cross-lagged prospective associations between Executive Function and depressive symptoms to be adjusted by wave 6 levels in order to examine change over

time. Significant synchronous associations between EF1-D1 or EF2-D2 in the absence of other associations would indicate that the relationships between Executive Function and depressive symptoms may be epiphenomenal, but not indicative of predictive change. Significant associations for only one of the cross-lagged paths imply a model of unidirectional change over 5-years. Significant associations between the auto-correlations of D1-D2 and EF1-EF2, but not between the associations of the cross-lags (EF1-D2 and EF1-D2) would indicate that Executive Function and depressive symptoms are causally unassociated. Lastly, if the cross-lag of EF1-D2 > D1-EF2 then Executive Function predicts depressive symptoms more than depressive symptoms predicts Executive Function.

Figure 2.2 Simplified Model of Cross-Lagged Panel Design



D1 and D2 are depressive symptoms at wave 6 and wave 7 respectively. EF1 and EF2 are Executive Function at wave 6 and wave 7 respectively. Straight lines represent regression paths and curved lines represent paths of covariation.

After models were identified for Executive Function and ZDI as independent predictors, we assessed the specificity of these relationships by substituting each

cognitive domain (Global composite, Visual-Spatial Memory and Organization, Verbal Episodic Memory, Scanning and Tracking, Working Memory) in the place of Executive Function to determine the specificity of these associations. Cognitive domains were measured as latent variables with subtest errors from wave 6 being covaried with subtest errors from wave 7. ZDI was measured as a continuous observed variable from the scoring scheme above. Pathways were assessed first in the presence of basic covariates (age, sex, education, ethnicity, and marital status) and then in the presence of an extended set of covariates.

2.5.3 Conditional Mediation Analyses

After the temporal precedence of Executive Function and depressive symptoms was determined via CLPD analysis, the direct effects of wave 6 APOE-E4 genotype x age x tHcy interactions on wave 7 depressive symptoms adjusted for wave 6 depressive symptoms was examined. Simultaneously, we examined the indirect associations of these three-way interactions and depressive symptoms through Executive Function. All conditional mediation models were also adjusted for lower-order two-way interactions and their respective main effects in addition to model covariates from the CLPD. Since tHcy was of primary interest in these models, the direct and indirect (through Executive Function/cognitive function) effects of tHcy on depressive symptoms were included in the conditional mediation tables below. As was true for the CLPD analyses above, we substituted each cognitive domain individually in the place of Executive Function in these models to determine the specificity of these associations.

We estimated the parameters of our models from eligible participants with data at wave 6 and wave 7 using maximum likelihood estimation for all analyses (CLPD EF

Extended models, 21.1% any missing data; Conditional Mediation EF Extended models 9.0% any missing data). Standard errors and confidence intervals were estimated using SPSS V.24 AMOS software bootstrapping techniques (5000 samples).

3. RESULTS

3.1 Attrition, Demographic, and Health Variables

Table 3.1 shows demographic and health characteristics at wave 6 for participants who completed both wave 6 and wave 7 (*n* = 719) and those who only completed wave 6 because they were either unavailable (*n* = 103) or not invited back (*n* = 196) for wave 7 analyses due to living outside of the Central New York area. Compared with those that only completed wave 6 (*n* = 299), a lower proportion of those that completed both waves were Black, were previously diagnosed with depression, and were marginally less likely to be diabetic or taking psychotropic medications (*p*'s < .05). Additionally, those that completed both waves had higher levels of functional performance and marginally higher total cholesterol as well as lower levels of depressive symptoms (ZDI), tHcy, and HDL (*p*'s < .10). Lastly, those that completed both waves performed better across all domains of cognitive performance (*p*'s < .01).

Table 3.1 Wave 6 Demographic and Health Characteristics

Variable	Participation Period		*P*-value
	Wave 6 only *n* = 299	Both Waves *n* = 719	
Age (years), M(SD)[1]	62.31(14.77)	62.09(11.93)	
Sex (% female)	55.6	59.7	
Education (years), M(SD)	14.52(2.84)	14.64(2.71)	
Ethnicity (% Black)	10.7	6.1	*
Marital Status (% Cohabitating/Married)	59.1	64.7	
Recent Life Events (%)	23.0	22.0	
Social Activity, M(SD)[1]	20.81(5.94)	21.19(5.17)	
Cohabitation (% living w/ others)	76.0	77.5	
Close Relationships, M(SD)	6.48(9.43)	6.39(6.63)	
Functional Performance M(SD)[1]	1.17(1.26)	0.84(1.23)	***
Zung Depression Inventory M(SD)	44.01(9.38)	41.87(9.42)	**
Cigarettes/week, M(SD)[1]	11.94(43.06)	8.48(34.06)	
Alcohol drinks/week, M(SD)	1.64(3.74)	1.47(2.54)	
Body Mass Index, M(SD)	29.43(6.12)	29.18(5.84)	
Homocysteine(µmol/L), M(SD)[1]	10.69(4.56)	9.66(3.14)	**
B12, nmol/L, M(SD)[1]	485.03(291.78)	475.20(233.94)	
B6, nmol/L M(SD)[1]	97.54 (105.15)	92.01(84.78)	
B9, ng/L M(SD)[1]	15.82(5.87)	15.24(5.30)	
C-Reactive Protein, M(SD)	4.38(4.65)	3.99(4.55)	
Mean Arterial Pressure, M(SD)	91.28(12.47)	90.50(12.74)	
Total Cholesterol (Mg/DL), M(SD)	197.26(41.94)	202.82(39.44)	+
HDL, mg/DL, M(SD)	51.85(14.79)	53.88(15.41)	+
LDL, mg/DL, M(SD)	118.34(33.94)	121.18(33.07)	
Triglycerides, mg/DL, M(SD)	146.67(123.98)	142.95(108.11)	
EPI-GFR, ml/min, M(SD)[1]	76.11(21.04)	77.86(16.43)	
Framingham Score, M(SD)	13.45(6.04)	13.12(5.62)	
Hypertension Meds (%)	55.0	51.0	
Psychotropic Meds (%)	25.0	15.0	***
Diabetes (%)	16.0	11.0	+
Previous Depression Diagnosis (%)	20.0	12.0	*
Cardiovascular Disease (%)	15.4	12.8	
APOE-E4 (%)	23.3	28.0	
Global Composite, M(SD)[1]	-0.14(1.04)	0.12(0.89)	***
Verbal Episodic Memory, M(SD)[1]	-0.13(1.07)	0.10(0.90)	**
Visual Spatial Organization and Memory, M(SD)[1]	-.12(1.21)	0.10(0.92)	**
Scanning and Tracking, M(SD)[1]	-0.10(1.02)	0.10(0.93)	**
Working Memory, M(SD)	-.11(1.01)	0.09(0.95)	**
Expanded Executive Function Composite, M(SD)[1]	-0.14(1.03)	0.10(0.93)	**

+ $p < .10$, *$p < .05$, ** $p < .01$ *** $p < .001$
[1]Equal variances not assumed
Categorical variables assessed with Fisher's exact test
Cognitive Performance measured in z-score units

3.2 Associations of Executive Function and other Domains

As expected, significant associations between the wave 6 Expanded Executive Function composite and all other domains of cognitive performance were observed (*p*'s < .001). Rather than emerging as an orthogonal construct, Executive Function was highly associated with Global cognitive performance, Visual-Spatial Organization and Memory (*r*'s > 0.80) and was moderately associated with Verbal Episodic Memory, Working Memory, and Scanning and Tracking (0.20 < *r*'s < 0.80). Lastly, Executive Function was moderately associated with the Similarities subtest which has been shown in prior MSLS analyses to load significantly across all cognitive domains (Elias et al., 2006). Table 3.2 displays zero-order correlations for all wave 6 domains of cognitive performance.

Table 3.2 Zero-Order Correlations of Wave 6 Cognitive Domains

Wave 6 Variable	Executive Function	Global	Verbal Episodic Memory	Working Memory	Scanning & Tracking	VSOM
Executive Function	-	0.887***	0.472***	0.645***	0.740***	0.847***
Global		-	0.692***	0.711***	0.839***	0.886***
Verbal Episodic Memory			-	0.391***	0.437***	0.504***
Working Memory				-	0.500***	0.448***
Scanning & Tracking					-	0.690***
VSOM						-
Similarities	0.612***	0.663***	0.442***	0.387***	0.452***	0.612***

***p<.001, **p<.01, *p<.05 +p<.10

3.3 Covariate Selection

The following variables measured at wave 6 and wave 7 were considered based on the their common inclusion in the literature: age, sex, education, marital status, ethnicity, diabetes mellitus status, CVD status, Framingham CVD Risk Score, social activity, number of close relationships, smoking, cohabitation, measures of obesity, alcohol consumption, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, total cholesterol (TC), estimated glomular filtration rate/creatinine, vitamins B6/B9/B12, hypertension status and continuously measured systolic/diastolic blood pressure, physical function deficits (Dearborn, Robbins, & Elias, 2015), psychotropic medications/anti-depressive medications, and previous depression diagnosis requiring treatment (Appendix B).

Of the variables considered above, measures of hypertension, smoking, estimated glomular filtration rate/creatinine, vitamins B9/B12, HDL, TC, triglycerides, and smoking were dropped due to lack of associations with depressive symptoms (*p*'s > .10). Measures of obesity, psychotropic/anti-depressive medications, and previous depression diagnosis requiring treatment were dropped due to lack of associations with Executive Function (*p*'s > .10). Alcohol consumption, cohabitation status, number of close relationships, social activity, and LDL were dropped due to lack of associations with tHcy (*p*'s > .10).

Table 3.3 shows model covariates surviving backward elimination. Physical function deficits, diabetes mellitus status, vitamin B6, and CVD status were considered for analysis based on their associations with Executive Function, depressive symptoms

and tHcy, but were ultimately dropped because they did not contribute significantly to model fit.

Table 3.3 Zero-Order Associations of Model Covariates Surviving Backward Elimination

Wave 6 Variable	tHcy	Age	Sex	Education	Marital Status	Ethnicity	Framingham
Executive Function	-0.151***	-0.394***	-0.020	0.386***	0.188***	-0.266***	-0.355***
Global	-0.194***	-0.491***	0.073+	0.390***	0.185***	-0.185***	-0.442***
Verbal Episodic Memory	-0.116**	-0.361***	0.124**	0.237***	0.057	-0.143***	-0.305***
Working Memory	-0.106**	-0.217***	0.052	0.278***	0.096*	-0.214***	-0.256***
Scanning & Tracking	-0.234***	-0.523***	0.138***	0.307***	0.145***	-0.229***	-0.444***
VSOM	-0.154***	-0.462***	-0.017	0.340***	0.231***	-0.245***	-0.390***
ZDI	0.066+	0.090*	0.091*	-0.191***	-0.153***	0.073+	0.069+
tHcy	-	0.200***	-0.261***	-0.052	0.058	0.077*	0.289***

***p<.001, **p<.01, *p<.05 +p<.10
Wave 7 ZDI (tHcy r = 0.088, p = .023; Framingham r = 0.100, p = .010)

3.4 Cross-Sectional Associations of Cognitive Performance and Depressive Symptoms

After adjustment for basic demographic covariates (Basic model: age, sex, education, ethnicity, and marital status) and cardiovascular risk factors (Extended model: tHcy and Framingham Risk Score), Executive Function was associated inversely with depressive symptom severity (Table 3.4). Additionally, all other domains of cognitive performance were associated inversely (p's < .05) with depressive symptom severity with the exception of Working Memory (p > .10). These wave 6 model

covariates were employed in the prospective CLPD based on the methods described above.

Table 3.4 Cross-Sectional Standardized (β) and Unstandardized (b) Regression Coefficients of Wave 6 Cognitive Function Predicting Symptoms of Depression

	Basic Model			Extended Model		
Cognitive Outcome	β	b	SE	β	b	SE
Executive Function	-0.149***	-0.012***	0.003	-0.146***	-0.012***	0.003
Global	-0.157***	-0.005***	0.001	-0.156***	-0.005***	0.001
Verbal Episodic Memory	-0.077*	-0.007*	0.003	-0.078*	-0.007*	0.003
Working Memory	-0.022	-0.001	0.003	-0.022	-0.001	0.003
Scanning & Tracking	-0.140***	-0.011***	0.002	-0.137***	-0.011***	0.002
VSOM	-0.169***	-0.013***	0.002	-0.169***	-0.013***	0.002

***p <.001; * *p < 0.01; *p < 0.05

Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI
Extended model = Basic model + homocysteine, + Framingham Risk Score

3.5 5-year Cross-Lagged Associations of Cognitive Performance and Depressive Symptoms

CLPD model fit statistics illustrated in Figure 2.2 are displayed in Table 3.5 below. Although model χ2 statistics were significant across all cognitive domain models, RMSEA statistics range from excellent (Executive Function and Scanning and Tracking RMSEA's ≤ .05) to satisfactory (Global, Working Memory, Verbal Episodic Memory, Visual Spatial Organization and Memory (RMSEA's ≥ .06 < .09). These fit statistics were similar across other measures of fit (CFI and χ2/*df*) with the exception of Global cognitive performance models (CFI- Basic model = 0.811, CFI-Extended model

= 0.816), which likely suffered from the comparatively larger number (*n* = 17) and variability of subtests in the Global composite.

Table 3.5 Model Fit Statistics for 5-Year Cross-Lagged Panel Analyses

	CFI (Basic/Extended)	RMSEA (Basic/Extended)	χ2(df) (Basic/Extended)	p-value (all)
Executive Function	0.979 / 0.979	0.044 / 0.034	139.142(58) / 161.840(70)	<0.001
Global	0.811 / 0.816	0.080 / 0.077	4539.375(814) / 4648.440(882)	<0.001
Working Memory	0.945 / 0.954	0.065 / 0.060	235.583(58) / 248.316(70)	<0.001
Verbal Episodic Memory	0.955 / 0.962	0.086 / 0.076	213.055(34) / 216.637(42)	<0.001
Scanning and Tracking	0.983 / 0.984	0.047 / 0.044	166.133(58) / 166.777(70)	<0.001
VSOM	0.937 / 0.940	0.069 / 0.066	521.986(118) / 573.539(138)	<0.001

Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI
Extended model = Basic model + homocysteine, + Framingham Risk Score
CFI = Confirmatory Fit Index
RMSEA = Root Mean Squared Error of Approximation

3.5.1 Cognitive Function and Changes in Depressive Symptoms

After adjustment for wave 6 depressive symptom severity, demographic covariates (Basic) and cardiovascular risk factors (Extended), lower wave 6 Executive Function predicted increased depressive symptom severity at wave 7 ($p < .05$). This pattern of results was similar across other wave 6 domains of cognitive functioning, including Global cognitive performance, Scanning and Tracking, and Visual-Spatial Reasoning and Memory (p's < .05; VSOM Extended model $p < .10$). However, unlike Executive Function, wave 6 Verbal Episodic Memory and Working Memory failed to predict changes in depressive symptoms at wave 7. These results are displayed in

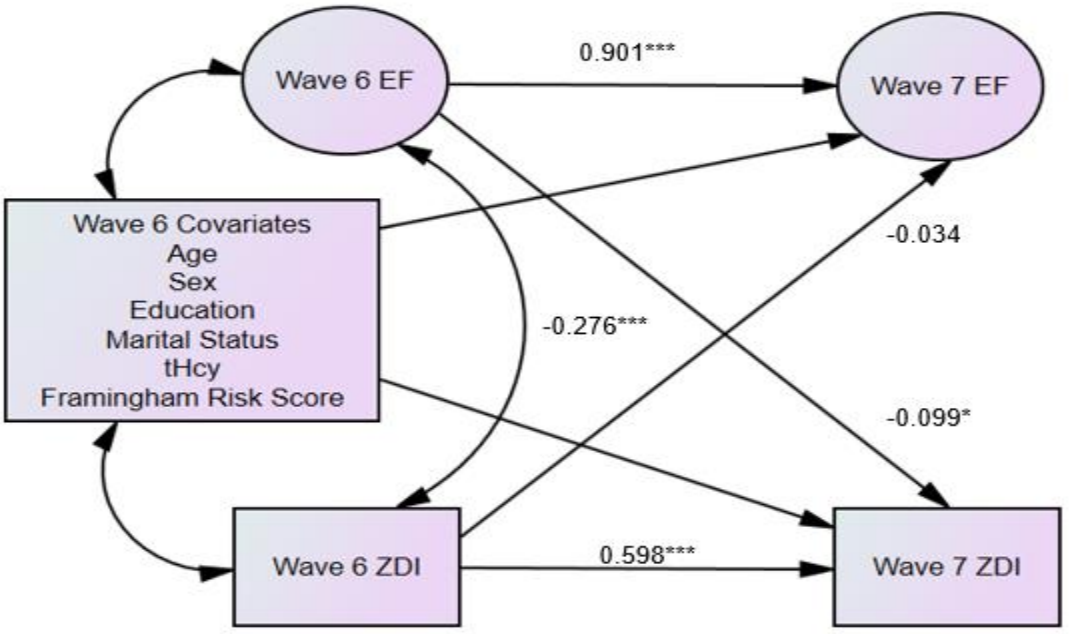
Table 3.6 below. Additionally, a simplified version of the Executive Function CLPD Extended Model is displayed in Figure 3.1 below. CLPD figures for the other remaining cognitive domains are displayed in Appendix D.

Table 3.6 Cross-Lagged Standardized (β) and Unstandardized (b) Regression Coefficients of Wave 6 Cognitive Function and Wave 7 Symptoms of Depression

	Basic Model			Extended Model		
Cognitive Outcome	β	b	SE	β	b	SE
Executive Function	-0.108*	-1.348*	0.613	-0.099*	-1.241*	0.614
Global	-0.136**	-4.587**	1.658	-0.130**	-4.383**	1.653
Verbal Episodic Memory	-0.044	-0.474	0.365	-0.046	-0.493	0.364
Working Memory	-0.027	-0.427	0.605	-0.024	-0.319	0.605
Scanning & Tracking	-0.170***	-2.188***	0.599	-0.167***	-2.145***	0.598
VSOM	-0.093*	-1.189*	0.572	-0.086+	-1.107+	0.572

***p < .001; * *p < 0.01; *p < 0.05, p < .10
Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI
Extended model = Basic model + homocysteine, + Framingham Risk Score

Figure 3.1 Cross-Lagged Panel Analysis Executive Function Extended Model



Fit Indices
RMSE = 0.034
$\chi 2(70) = 161.840$, $p < .001$
$\chi 2/df = 2.312$
CFI = 0.979

3.5.2 Depressive Symptoms and Changes in Cognitive Function

These CLPD analyses were conducted simultaneously with those presented Table 3.6 with adjustment for wave 6 Executive Function to determine the 5-year predictive value of wave 6 depressive symptoms on changes in Executive Function at wave 7. These analyses were repeated in separate models with adjustment for all other wave 6 domains of cognitive function. After adjustment for demographic covariates (Basic) and cardiovascular risk factors (Extended), wave 6 depressive symptoms failed to predict changes in Executive Function at wave 7 ($p < .05$). Similarly, wave 6 depressive symptoms failed to predict changes in wave 7 Global cognitive performance and Visual-Spatial Organization and Memory, and Verbal Episodic Memory (p's > .05). However, unlike Executive Function, higher wave 6 depressive symptoms were associated with decreased performance in wave 7 Working Memory and Scanning and Tracking (p's < .05). These results are presented in Table 3.7 below.

Table 3.7 Cross-lagged Standardized (β) and Unstandardized (b) Regression Coefficients of Wave 6 Symptoms of Depression and Wave 7 Cognitive Function

	Basic Model			Extended Model		
Cognitive Outcome	β	b	SE	β	b	SE
Executive Function	-0.031	-.003	.002	-0.034	-0.003	0.002
Global	-0.020	-0.001	0.001	-0.022	-0.001	0.001
Verbal Episodic Memory	-0.049^{+}	-0.005^{+}	0.003	-0.047^{+}	-0.005^{+}	0.003
Working Memory	-0.084**	-0.005**	0.002	-0.086**	-0.006**	0.002
Scanning & Tracking	-0.040*	-0.003*	0.002	-0.042*	-0.004*	0.002
VSOM	-0.003	0.000	0.002	-0.005	0.000	0.002

* *p < 0.01; *p < 0.05; + p < .10
Basic model = wave 6 age, sex, education, ethnicity, marital status
Extended model = Basic model + homocysteine, + Framingham Risk Score

3.5.3 Directional Findings of Cross-Lagged Panel Analyses

The results suggest significant unidirectional relationships with lower wave 6 Executive Function predicting increases in depressive symptoms at wave 7, but wave 6 depressive symptoms not predicting changes in wave 7 Executive Function. Similar unidirectional results were found for Global cognitive performance, and Visual-Spatial Organization and Memory. Different unidirectional patterns were found for Working Memory, with higher wave 6 depressive symptoms predicting increases in wave 7 Working Memory. Lastly an inverse bidirectional trend was observed between Scanning and Tracking and depressive symptoms, though wave 6 Scanning and Tracking was a stronger predictor (Extended model: βstd = -0.167) of changes in wave 7 depressive symptoms compared with wave 6 depressive symptoms as a predictor of changes in wave 7 Scanning and Tracking (Extended model: βstd = -0.042).

3.6 Conditional (Moderated by Age x APOE-E4) Effects of Homocysteine Mediated Through Cognitive Function on Wave 7 Depressive Symptoms

Figure 3.2 and Figure 3.3 show simplified models of individual component path coefficients for predicting wave 7 depressive symptoms from which direct, indirect, and total effects can be calculated for the Basic and Extended model, respectively. Basic wave 6 model covariates and wave 6 depressive symptoms were repeated from CLPD analyses and Extended models included adjustments for wave 6 Framingham Risk Score. Table 3.8 and Table 3.9 show the direct and indirect effects of tHcy, Framingham Risk Score, and age x tHcy x APOE-E4 genotype interactions (adjusted for all corresponding two-way interactions) in relation to wave 6 Executive Function, other domains of cognitive performance, and wave 7 depressive symptoms for the Basic and

Extended model, respectively. In all mediation analyses, age and tHcy were Z-transformed for clarity of interpretation.

Model $\chi 2$ statistics remained significant across all cognitive domain models and RMSEA statistics again ranged from excellent (Executive Function and Scanning and Tracking RMSEA's ≤ .05) to adequate (Working Memory, Verbal Episodic Memory, and Visual-Spatial Organization and Memory RMSEA's ≤ .073) with the exception again of Global performance models (Extended model RMSEA = .097).

3.6.1 Age x tHcy x APOE-E4 Effects

For both the Basic and Extended models, the direct paths of wave 6 tHcy x age x APOE-E4 interaction were significantly associated with changes in wave 7 depressive symptoms across all cognitive models (*p*'s < .01, Executive Function *p* < .05). However, wave 6 tHcy x age x APOE-E4 interactions were unrelated to wave 6 performance across all cognitive domains. Lastly the indirect paths from wave 6 age x tHcy x APOE-E4 interaction to changes in wave 7 depressive symptoms as mediated by cognitive performance were not significantly different from zero in all models (*p*'s > .05) with the exception of Scanning and Tracking (*p* < .05).

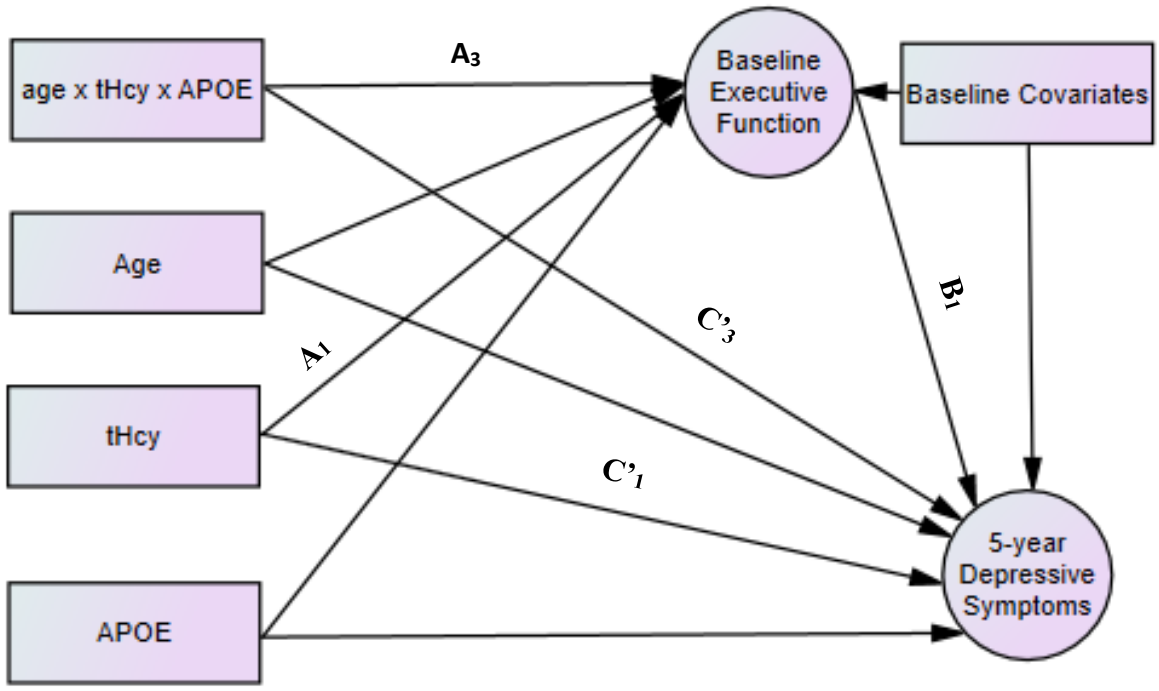
3.6.2 tHcy Effects

The main effect of wave 6 tHcy was not associated with changes in wave 7 depressive symptoms or wave 6 cognitive performance across all models (*p*'s > .10). Additionally, no mediation of the indirect path from wave 6 tHcy to wave 7 changes in depressive symptoms was observed for any cognitive domains (*p*'s > .10).

3.6.3 Framingham Risk Score Effects

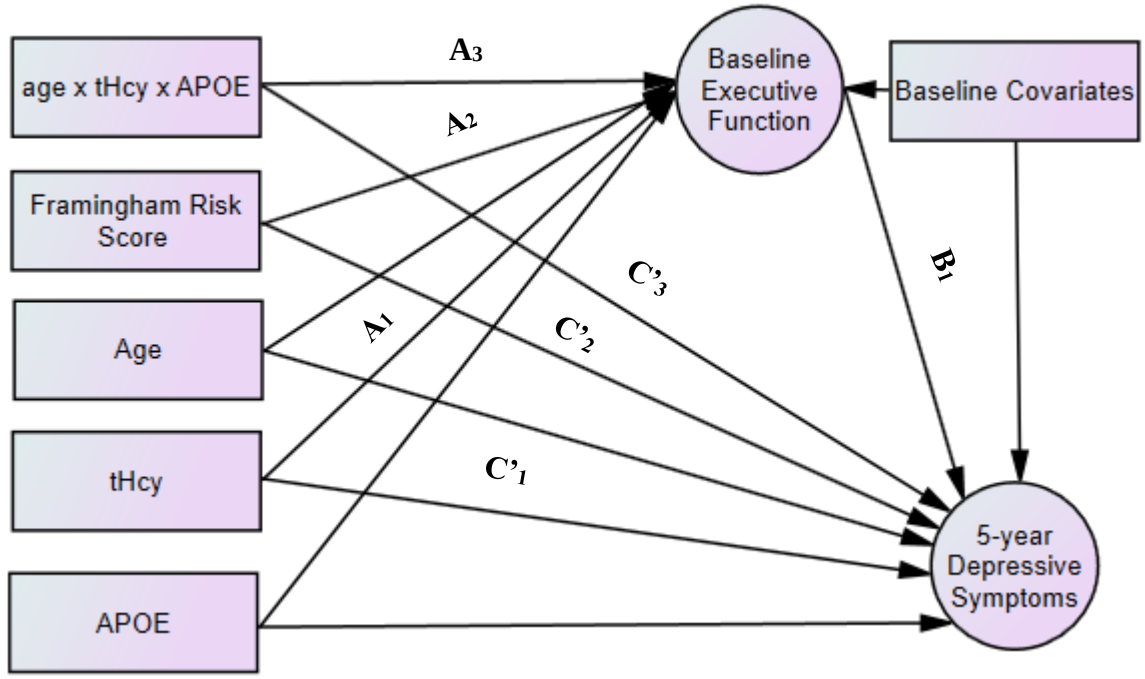
Wave 6 Framingham Risk Score was positively associated with changes in wave 7 depressive symptoms in all cognitive models (p's < .05; Global $p < .10$) with the exception of Executive Function ($p > .10$). Additionally, wave 6 Framingham Risk Score was inversely associated with wave 6 Executive Function ($p < .01$), Working Memory, Visual Spatial Organization and Memory (p's < .05), and marginally inversely associated with wave 6 Global cognitive performance ($p < .10$). Additionally, no mediation of the indirect path from wave 6 Framingham Risk Score to wave 7 changes in depressive symptoms was observed for any cognitive domains (p's > .10), with the exception of Global cognitive performance ($p < .05$).

Figure 3.2 Simplified Path Basic Model Showing Conditional Indirect Effects of tHcy (Moderated by Age and APOE-E4) on Symptoms of Depression



Lower-order two-way interactions (age x tHcy, age x APOE-E4 & tHcy x APOE-E4) adjusted with wave 6 covariates

Figure 3.3 Simplified Path Extended Model Showing Conditional Indirect Effects of tHcy (Moderated by Age and APOE-E4) on Symptoms of Depression



Lower-order two-way interactions (age x tHcy, age x APOE-E4 & tHcy x APOE-E4) adjusted with wave 6 covariates

Table 3.8 Component Path Coefficients (b) For the Direct and Indirect Effects of Age, tHcy, and APOE-E4 on Symptoms of Depression Mediated through Cognitive Function (Basic Model).

		Direct Effect Component Path			Indirect Effect Component Path			Indirect Effect	
Cognitive Outcome		c'_1	c'_3		a_1	a_3	b_1	ab_1	ab_3
Executive Function	b	0.056	-2.433**		0.007	0.053	-0.939	-0.006	-0.049
	se	0.520	0.811		0.050	0.094	0.735	0.062	0.121
Global	b	0.060	-2.313**		0.004	0.039	-3.755*	-0.041	-0.146
	se	0.519	-0.812		0.029	0.013	1.808	0.054	0.139
Verbal Episodic Memory	b	0.070	-2.376**		0.041	0.066	-0.410	-0.017	-0.027
	se	0.508	0.804		0.039	0.096	0.408	0.063	0.028
Working Memory	b	0.052	-2.514**		0.043	0.062	0.033	0.002	0.001
	se	0.511	0.805		0.035	0.082	0.636	0.036	0.069
Scanning & Tracking	b	0.010	-2.199*		-0.024	0.167	-1.850**	0.044	-0.309*
	se	0.515	0.809		0.033	0.079	0.622	0.067	0.184
VSOM	b	0.063	-2.446**		0.016	0.028	-0.962	-0.015	-0.027
	se	0.517	0.807		0.039	0.082	0.642	0.047	0.098

* *p < 0.01; *p < 0.05; +p < .10

Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI
C'_1 = Direct effect of tHcy on wave 7 ZDI unmediated by cognitive function
C'_3 = Direct effect of tHcy x age x APOE-E4 interaction on wave 7 ZDI unmediated by cognitive function
A_1 = Indirect component effect of tHcy on cognitive function
A_3 = Indirect component effect of tHcy x age x APOE-E4 interaction on cognitive function
Ab_1 = Indirect effect of tHcy on ZDI 7 mediated through cognitive function
Ab_3 = Indirect effect of tHcy x age x APOE-E4 interaction on ZDI 7 mediated through cognitive function
B_1 = Indirect component effect of wave 6 cognitive function on wave 7 ZDI

Table 3.9 Component Path Coefficients (b) For the Direct and Indirect Effects of Age, tHcy, and APOE-E4 on Symptoms of Depression Mediated through Cognitive Function (Extended Model).

		Direct Effect Component Path				Indirect Effect Component Path				Indirect Effect		
Cognitive Outcome		c'_1	c'_2	c'_3		a_1	a_2	a_3	b_1	ab_1	ab_2	ab_3
Executive Function	b	0.015	0.144	-2.049**		0.007	-0.017**	0.055	-0.809	-0.012	0.014	-0.044
	se	0.514	0.077	0.815		0.051	0.007	0.092	0.736	0.058	0.015	0.111
Global	b	-0.008	0.143+	-2.343**		0.006	-0.004+	0.040	-3.518*	-0.021	0.014*	-0.139
	se	0.513	0.076	0.817		0.013	0.002	0.029	1.793	0.053	0.010	0.133
Verbal Episodic Memory	b	-0.006	0.162*	-2.104**		0.039	0.003	0.066	-0.422	-0.017	-0.001	-0.028
	se	0.501	0.076	0.808		0.039	0.008	0.095	0.412	0.028	0.005	0.064
Working Memory	b	-0.029	0.163*	-2.546**		0.050	-0.015*	0.064	0.159	0.008	-0.002	0.010
	se	0.504	0.077	0.808		0.035	0.006	0.080	0.637	0.040	0.010	0.070
Scanning & Tracking	b	-0.061	0.151*	-2.223*		-0.022	-0.004	0.167*	-1.816**	-0.023	0.008	-0.304*
	se	0.509	0.077	0.813		0.033	0.006	0.079	0.617	0.066	0.012	0.182
VSOM	b	-0.007	0.146*	-2.471**		0.021	-0.012*	0.029	-0.863	-0.018	0.010	-0.025
	se	0.511	0.076	0.811		0.040	0.006	0.081	0.641	0.046	0.010	0.081

* *p < 0.01; *p < 0.05; +p < .10

Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI

Extended model = Basic model + Framingham Risk Score

C'_1 = Direct effect of tHcy on wave 7 ZDI unmediated by cognitive function

C'_2 = Direct effect of Framingham Risk Score on wave 7 ZDI unmediated by cognitive function

C'_3 = Direct effect of tHcy x age x APOE-E4 interaction on wave 7 ZDI unmediated by cognitive function

A_1 = Indirect component effect of tHcy on cognitive function

A_2 = Indirect component effect of Framingham Risk Score on cognitive function

A_3 = Indirect component effect of tHcy x age x APOE-E4 interaction on cognitive function

Ab_1 = Indirect effect of tHcy on ZDI 7 mediated through cognitive function

Ab_2 = Indirect effect of Framingham Risk Score on ZDI 7 mediated through cognitive function

Ab_3 = Indirect effect of tHcy x age x APOE-E4 interaction on ZDI 7 mediated through cognitive function

B_1 = Indirect component effect of wave 6 cognitive function on wave 7 ZDI

3.7 Conditional Effects of Wave 6 Homocysteine (Moderated by Age) on Wave 7 Depressive Symptoms Mediated Through Cognitive Function

Due to significant three-way interactions between age, tHcy and APOE-E4 genotype, mediation path analyses were conducted separately for APOE-E4 carriers (n = 189) and non-carriers (n = 483). Basic and Extended model covariates were repeated from the above mediation analyses with adjustment for the main effects of age and tHcy in determining the associations of tHcy x age interactions, cognitive function, and wave 7 depressive symptoms. Overall model fit statistics will be addressed, followed by conditional mediation analyses by APOE-E4 genotype.

3.7.1 Model Fit Statistics

Prior model fit analyses were conducted with the combined statistical power of APOE-E4 carriers and non-carriers combined (*n* = 719), resulting in significant $\chi 2$ statistics, indicating that the data were significantly different from what would be expected. Although in APOE-E4 carrier (n = 189) Extended models $\chi 2$ statistics remained significant, the Executive Function Extended model was not significantly different from model expectations ($p > 0.05$). Additionally, RMSEA statistics indicated excellent (Executive Function RMSEA = 0.028) to adequate fit (RMSEA's ≤ 0.076) with the exception of the Global Composite models (RMSEA = 0.112). Since there were considerably more APOE-E4 non-carriers in our sample (n = 483), Extended model $\chi 2$ statistics remained significant across all domains. However, RMSEA's were in the excellent (Executive Function RMSEA = 0.049) to adequate range (RMSEA's ≤ 0.076) with the exception of the Global Composite and Working Memory models (RMSEA's ≤ 0.108).

3.7.2 APOE-E4 Carriers – Age x tHcy Interaction Effects

Among APOE-E4 carriers in the Basic model (Table 3.10), significant associations were observed for the direct path of wave 6 age x tHcy interactions to changes in wave 7 depressive symptoms for the Visual-Spatial Organization and Memory and Working Memory models (*p*'s < .05). However, in the Extended models (Table 3.11), these direct associations fell to marginal significance for across all cognitive models (*p*'s < .10) with the exception of Scanning and Tracking (*p* > .10). In the Basic and Extended models, wave 6 age x tHcy interactions were not associated with wave 6 performance for any cognitive domain, nor did any domain of cognitive performance significantly mediate the indirect association of wave 6 age x tHcy interactions and changes in wave 7 depressive symptoms *(p*'s > .10; Basic model Executive Function *p* < .10).

3.7.3 APOE-E4 Carriers – tHcy Effects

For both the Basic and Extended models for APOE-E4 carriers (Table 3.10 and Table 3.11), wave 6 tHcy was not associated with wave 6 performance for any cognitive domain (*p*'s > .10). Additionally, wave 6 tHcy failed to predict changes in wave 7 depressive symptoms. Lastly, the indirect path from wave 6 tHcy and changes in wave 7 depressive symptoms was not significantly mediated by any cognitive domain (*p*'s >.10).

3.7.4 APOE-E4 Carriers – Framingham Risk Score Effects

For APOE-E4 carriers, wave 6 Framingham Risk Score was inversely associated with Global cognitive performance and Working Memory (*p*'s < .05; Table 3.11) and

marginally inversely associated with Executive Function ($p < .10$). However, wave 6 Framingham Risk Score failed to predict changes in wave 7 depressive symptoms. Lastly, the path from wave 6 Framingham Risk Score to changes in wave 7 depressive symptoms was not significantly mediated by any domain of cognitive performance (p's > .10).

3.7.5 APOE-E4 Non-Carriers – Age x tHcy Interaction Effects

Among APOE-E4 non-carriers in the Extended models (Table 3.13), significant positive associations between wave 6 tHcy x age and changes in wave 7 depressive symptoms were observed across all cognitive models (p's < .05; Global $p < .10$). However, wave 6 tHcy x age interactions failed to significantly predict wave 6 cognitive performance in all cognitive models with the exception of Scanning in Tracking (Table 3.12 Basic model $p < .05$) and Global cognitive performance (Basic model $p < .10$; Extended model $p < .05$). Lastly, the path from wave 6 age x interactions to changes in wave 7 depressive symptoms was not significantly mediated by any domain of cognitive performance (p's > .10) with the exceptions of Scanning and Tracking (Basic and Extended model p's < .05) and Global cognitive performance (Basic and Extended model p's < .10).

3.7.6 APOE-E4 Non-Carriers – tHcy Effects

For both the Basic and Extended models for APOE-E4 non-carriers (Table 3.12 and Table 3.13), wave 6 tHcy was not associated with wave 6 performance for any cognitive domain (p's > .10) with the exception of Scanning and Tracking (Extended model $p < .05$). Additionally, wave 6 tHcy failed to predict changes in wave 7

depressive symptoms across all cognitive models (*p*'s > .10). Lastly, the path from wave 6 tHcy and changes in wave 7 depressive symptoms was not significantly mediated by any cognitive domain (*p*'s >.10).

3.7.7 APOE-E4 Non-Carriers – Framingham Risk Score Effects

For APOE-E4 non-carriers, wave 6 Framingham Risk Score was not associated with performance in any cognitive domain (p's > .10) with the exception of Executive Function (Table 3.13; *p* < .10). Additionally, wave 6 Framingham Risk Score failed to predict changes in wave 7 depressive symptoms (*p*'s > .10). Lastly, the path from wave 6 Framingham Risk Score to changes in wave 7 depressive symptoms was not significantly mediated by any domain of cognitive performance (*p*'s > .10).

Table 3.10 Component Path Coefficients (b) for the Direct and Indirect Effects of Age and tHcy on Symptoms of Depression Mediated through Cognitive Function (Basic Model) for APOE-E4 Carriers

		Direct Effect Component Path			Indirect Effect Component Path			Indirect Effect	
Cognitive Outcome		c'_1	c'_3		a_1	a_3	b_1	ab_1	ab_3
Executive Function	b	0.450	-1.110		-0.068	0.025	-1.883	0.128	-0.046+
	se	0.662	0.643		0.075	0.084	1.377	0.208	0.203
Global	b	0.550	-1.106+		0.010	0.012	-3.860	0.040	-0.046
	se	0.648	0.622		0.027	0.028	3.501	0.138	0.141
Verbal Episodic Memory	b	0.566	-1.126+		-0.022	0.068	-0.466	0.010	-0.032
	se	0.654	0.616		0.087	0.082	0.763	0.075	0.094
Working Memory	b	0.592	-1.171*		-0.083	0.050	0.250	-0.021	0.013
	se	0.651	0.623		0.076	0.070	1.139	0.133	0.100
Scanning & Tracking	b	0.661	-0.964+		0.029	0.072	-2.664*	-0.078	-0.193
	se	0.637	0.616		0.065	0.067	1.264	0.196	0.215
VSOM	b	0.560	-1.160*		-0.027	-0.007	-1.100	0.029	0.007
	se	0.652	0.623		0.067	0.075	1.244	0.121	0.123

* *p < 0.01; *p < 0.05, +p < .10

N = 189
Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI
C'_1 = Direct effect of tHcy on wave 7 ZDI unmediated by cognitive function
C'_3 = Direct effect of tHcy x age interaction on wave 7 ZDI unmediated by cognitive function
A_1 = Indirect component effect of tHcy on cognitive function
A_3 = Indirect component effect of tHcy x age interaction on cognitive function
Ab_1 = Indirect effect of tHcy on ZDI 7 mediated through cognitive function
Ab_3 = Indirect effect of tHcy x age interaction on ZDI 7 mediated through cognitive function
B_1 = Indirect component effect of wave 6 cognitive function on wave 7 ZDI

Table 3.11 Component Path Coefficients (b) for the Direct and Indirect Effects of Age and tHcy on Symptoms of Depression Mediated through Cognitive Function (Extended Model) for APOE-E4 Carriers

		Direct Effect Component Path				Indirect Effect Component Path				Indirect Effect		
Cognitive Outcome		c'_1	c'_2	c'_3		a_1	a_2	a_3	b_1	ab_1	ab_2	ab_3
Executive Function	b	0.351	0.135	-1.067+		-0.048	-0.024+	0.016	-1.715	0.083	0.041	-0.027
	se	0.656	0.147	0.651		0.072	0.014	0.082	1.414	0.185	0.044	0.189
Global	b	0.626	0.145	-1.061+		-0.004	-0.008*	0.009	-3.401	0.013	0.028	-0.031
	se	0.644	0.143	0.629		0.026	0.005	0.027	3.486	0.122	0.030	0.129
Verbal Episodic Memory	b	0.420	0.178	-1.061+		-0.028	0.007	0.071	-0.485	0.014	-0.003	-0.034
	se	0.623	0.140	0.623		0.085	0.018	0.087	0.766	0.078	0.018	0.095
Working Memory	b	0.455	0.192	-1.117+		-0.057	-0.030*	0.039	0.522	-0.030	-0.016	0.020
	se	0.646	0.144	0.628		0.071	0.012	0.067	1.174	0.112	0.039	0.096
Scanning & Tracking	b	0.535	0.151	-0.916		0.037	-0.009	0.069	-2.570*	-0.096	0.024	-0.178
	se	0.637	0.143	0.624		0.065	0.010	0.067	1.275	0.191	0.031	0.210
VSOM	b	0.434	0.156	-1.104+		-0.012	-0.017	-0.013	-0.958	0.012	0.017	0.012
	se	0.646	0.143	0.631		0.065	0.013	0.074	1.258	0.110	0.029	0.117

* *p < 0.01; *p < 0.05, +p < .10
Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI
Extended model = Basic model + Framingham Risk Score
C'_1 = Direct effect of tHcy on wave 7 ZDI unmediated by cognitive function
C'_2 = Direct effect of Framingham Risk Score on wave 7 ZDI unmediated by cognitive function
C'_3 = Direct effect of tHcy x age interaction on wave 7 ZDI unmediated by cognitive function
A_1 = Indirect component effect of tHcy on cognitive function
A_2 = Indirect component effect of Framingham Risk Score on cognitive function
A_3 = Indirect component effect of tHcy x age interaction on cognitive function
Ab_1 = Indirect effect of tHcy on ZDI 7 mediated through cognitive function
Ab_2 = Indirect effect of Framingham Risk Score on ZDI 7 mediated through cognitive function
Ab_3 = Indirect effect of tHcy x age interaction on ZDI 7 mediated through cognitive function
B_1 = Indirect component effect of wave 6 cognitive function on wave 7 ZDI

Table 3.12 Component Path Coefficients (b) for the Direct and Indirect Effects of Age and tHcy on Symptoms of Depression Mediated through Cognitive Function (Basic Model) for APOE-E4 Non-Carriers

		Direct Effect Component Path			Indirect Effect Component Path			Indirect Effect	
Cognitive Outcome		c'_1	c'_3		a_1	a_3	b_1	ab_1	ab_3
Executive Function	b	0.094	1.034*		0.009	-0.027	-0.645	-0.006	0.018
	se	0.528	0.518		0.049	0.050	0.892	0.057	0.065
Global	b	0.092	0.946+		0.003	-0.022+	-3.995+	-0.011	0.087+
	se	0.530	0.517		0.012	0.015	2.483	0.054	0.083
Verbal Episodic Memory	b	0.108	1.055*		0.049	-0.029	-0.342	-0.017	0.010
	se	-0.519	0.517		0.038	0.049	0.485	0.033	0.034
Working Memory	b	0.098	1.064*		0.041	-0.006	-0.154	-0.006	0.001
	se	0.524	0.518		0.033	0.043	0.814	0.042	0.036
Scanning & Tracking	b	0.039	0.955+		-0.033	-0.074*	-1.587*	0.053	0.118*
	se	0.523	0.511		0.033	0.033	0.777	0.066	0.082
VSOM	b	0.099	1.004+		0.015	-0.031	-1.027	-0.016	0.032
	se	0.530	0.517		0.036	0.047	0.791	0.050	0.070

* *p < 0.01; *p < 0.05, p < .10

N = 483

Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI
C'_1 = Direct effect of tHcy on wave 7 ZDI unmediated by cognitive function
C'_3 = Direct effect of tHcy x age interaction on wave 7 ZDI unmediated by cognitive function
A_1 = Indirect component effect of tHcy on cognitive function
A_3 = Indirect component effect of tHcy x age interaction on cognitive function
Ab_1 = Indirect effect of tHcy on ZDI 7 mediated through cognitive function
Ab_3 = Indirect effect of tHcy x age interaction on ZDI 7 mediated through cognitive function
B_1 = Indirect component effect of wave 6 cognitive function on wave 7 ZDI

Table 3.13 Component Path Coefficients (b) for the Direct and Indirect Effects of Age and tHcy on Symptoms of Depression Mediated through Cognitive Function (Extended Model) for APOE-E4 Non-Carriers

		Direct Effect Component Path				Indirect Effect Component Path				Indirect Effect		
Cognitive Outcome		c'_1	c'_2	c'_3		a_1	a_2	a_3	b_1	ab_1	ab_2	ab_3
Executive Function	b	0.027	0.132	1.100*		0.016	-0.014+	-0.034	-0.539	-0.009	0.008	0.018
	se	0.526	0.091	0.517		0.050	0.008	0.050	0.889	0.056	0.016	0.064
Global	b	0.026	0.130	1.011+		0.004	-0.002	-0.023*	-3.827+	-0.015	0.009	0.088+
	se	0.527	0.091	0.517		0.012	0.002	0.015	2.460	0.054	0.011	0.082
Verbal Episodic Memory	b	0.037	0.140	1.119*		0.048	0.000	0.029	-0.340	-0.016	0.000	0.010
	se	0.517	0.091	0.517		0.039	0.009	0.049	0.489	0.033	0.006	0.034
Working Memory	b	0.025	0.140	1.131*		0.046	-0.010	-0.011	-0.068	-0.003	0.001	0.001
	se	0.521	0.092	0.518		0.034	0.007	0.044	0.816	0.046	0.010	0.037
Scanning & Tracking	b	-0.029	0.136	1.019*		-0.032*	-0.002	-0.075	-1.569*	0.051	-0.002	-0.073*
	se	0.522	0.091	0.512		0.034	0.007	0.034	0.772	0.066	0.013	0.083
VSOM	b	0.033	0.130	1.070*		0.020	-0.010	-0.036	-0.944	-0.019	0.009	0.034
	se	0.527	0.090	0.517		0.037	0.007	0.047	0.787	0.050	0.011	0.050

* *p < 0.01; *p < 0.05, + p < .10

N = 483

Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI
Extended model = Basic model + Framingham Risk Score
C'_1 = Direct effect of tHcy on wave 7 ZDI unmediated by cognitive function
C'_2 = Direct effect of Framingham Risk Score on wave 7 ZDI unmediated by cognitive function
C'_3 = Direct effect of tHcy x age interaction on wave 7 ZDI unmediated by cognitive function
A_1 = Indirect component effect of tHcy on cognitive function
A_2 = Indirect component effect of Framingham Risk Score on cognitive function
A_3 = Indirect component effect of tHcy x age interaction on cognitive function
Ab_1 = Indirect effect of tHcy on ZDI 7 mediated through cognitive function
Ab_2 = Indirect effect of Framingham Risk Score on ZDI 7 mediated through cognitive function
Ab_3 = Indirect effect of tHcy x age interaction on ZDI 7 mediated through cognitive function
B_1 = Indirect component effect of wave 6 cognitive function on wave 7 ZDI

3.8 Johnson-Neyman Moderation Analysis

In order to explore the continuous nature of age's moderation effect on the association between wave 6 tHcy and changes in wave 7 depressive symptoms, we employed the Johnson-Neyman technique (P. O. Johnson & Fay, 1950). Unlike traditional "pick a point" moderation analysis, which requires the investigator to analyze age categories according to arbitrary cut-off points to observe differential effects of the predictor variable (tHcy), the Johnson-Neyman technique uses the entirety of available data to estimate the age regions where the effects of wave 6 tHcy on changes in wave 7 depressive symptoms are statistically significant. In addition to specificity, this technique has the benefit of preserving statistical power compared with splitting the data according to arbitrary cut-off points. Due to the significant associations of the three-way interactions of wave 6 age x tHcy x APOE-E4 and changes in wave 7 depressive symptoms, the interaction of age x tHcy was analyzed separately for APOE-E4 carriers and non-carriers. Although age x tHcy interactions did not reach the level of significance in the APOE-E4-carrier Extended models, the marginal trend for age x tHcy interactions ($p < 0.10$) warranted further exploration as did the apparent inversion of the wave 6 age x tHcy interaction effect on changes in wave 7 depressive symptoms for APOE-E4 non-carriers.

Johnson-Neyman moderation analyses are shown in Table 3.14 for APOE-E4 non-carriers by 10^{th}, 25^{th}, 50^{th}, 75, and 90^{th} age percentile ranks. In the Basic model, the effect of wave 6 tHcy on changes in wave 7 depressive symptoms was significant ($p < .05$) for individuals ≥ 75.39 years of age. These results were similar for the Extended model with significant effects for individuals ≥ 74.33 years of age ($p < .05$), indicating

increases in symptoms of depression with higher levels of tHcy among older adults. Figure 3.4 shows the simple slope of wave 6 tHcy on changes in wave 7 depressive symptoms by age for APOE non-carriers for the extended model.

Table 3.14 Effects (b) of Wave 6 tHcy by Age Category on Wave 7 Symptoms of Depression for APOE-E4 Non-Carriers

	Basic Model		Extended Model	
Age	b	SE	b	SE
47	-1.245	0.865	-1.431	0.869
54	-0.636	0.616	-0.767	0.619
62	0.060	0.427	-0.008	0.429
71	0.843+	0.497	0.845+	0.498
78	1.452*	0.712	1.414*	0.678

* *p < 0.01; *p < 0.05, + p < .10

N = 483

Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI
Extended model = Basic model + Framingham Risk Score

Johnson-Neyman moderation analyses are shown in Table 3.15 for APOE-E4 carriers by 10th, 25th, 50th, 75, and 90th age percentile ranks as well. Age category cut offs differed slightly, but sensitivity analysis did not indicate any significant differences of mean age between the groups (MD = 1.650. SE = 1.018, p = .11) nor considerable differences in age variance (p > 0.25). As expected, no significant associations were observed for APOE-E4 carriers. However, there was a marginal association (p < .10) of higher wave 6 tHcy and increases in wave 7 depressive symptoms for adults ≤ 51 years of age in the Basic model and ≤ 45 years of age in the Extended model. Figure 3.5 shows the simple slope of wave 6 tHcy on changes in wave 7 depressive symptoms by age for APOE carriers for the extended model.

Table 3.15 Effects (b) of Wave 6 tHcy by Age Category on Wave 7 Symptoms of Depression for APOE-E4 Carriers

	Basic Model		Extended Model	
Age	b	SE	b	SE
45	2.192+	1.124	1.912+	1.140
51	1.645+	0.864	1.396	0.882
61	0.733	0.676	0.536	0.690
69	0.004	0.859	-0.153	0.865
77	-0.726	1.215	-0.841	1.215

* *p < 0.01; *p < 0.05, + p < .10

N = 189

Basic model = wave 6 age, sex, education, ethnicity, marital status, and ZDI
Extended model = Basic model + Framingham Risk Score

3.9 Sensitivity Analysis: Conditional Effects of Wave 6 Framingham Risk Score (Moderated by Age and APOE-E4) on Wave 7 Depressive Symptoms

Due to significant conditional effects of wave 6 tHcy on changes in wave 7 depressive symptoms (moderated by age and APOE-E4), we explored whether these same three-way interaction patterns held for Framingham Risk score (age x APOE-E4 x Framingham Risk Score). In a Basic model, we adjusted for wave 6 age, sex, education, ethnicity, and marital status as well as lower-order two-way interactions and main effects of APOE-E4 and Framingham Risk Score. In the Basic model, we did not observe a significant three-way interaction effect of age x APOE x Framingham Risk Score on changes in wave 7 depressive symptoms (b = -0.778, SE = 0.540, *p* = 0.16). These results remained similar with the addition of tHcy as a model covariate (b = -0.769, SE = 0.540, *p* = 0.16).

Figure 3.4 tHcy Effect Slope (b) and 95% Confidence Intervals by Age for APOE-E4 Non-Carriers

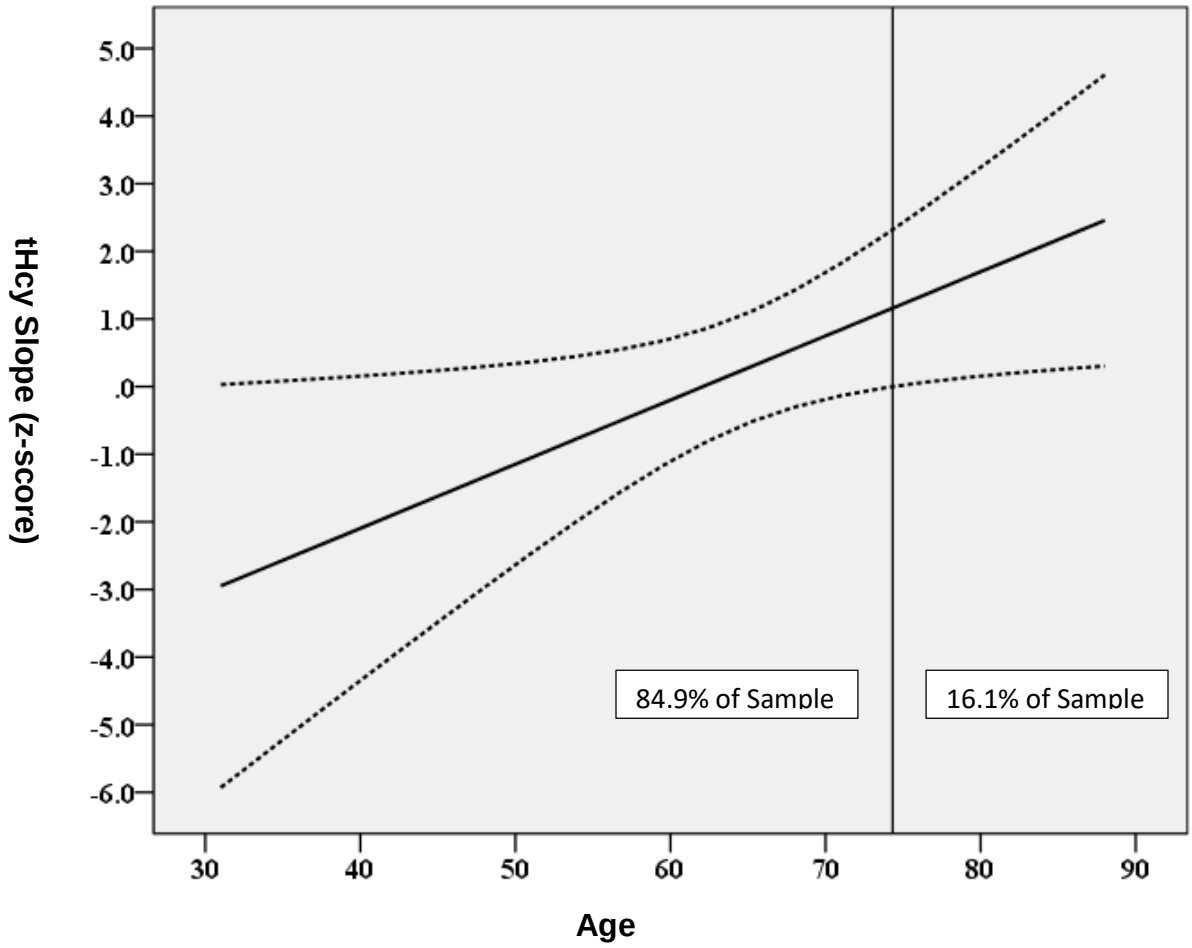


Figure obtained using Johnson-Neyman technique.

Solid vertical line represents area of significance ($p < 0.05$). Significant positive effects of wave 6 tHcy on wave 7 ZDI were found for individuals ≥ 74.33 years of age.

Adjusted for wave 6 age, sex, education, marital status, ZDI and Framingham Score

Figure 3.5 tHcy Effect Slope (b) and 95% Confidence Intervals by Age for APOE-E4 Carriers

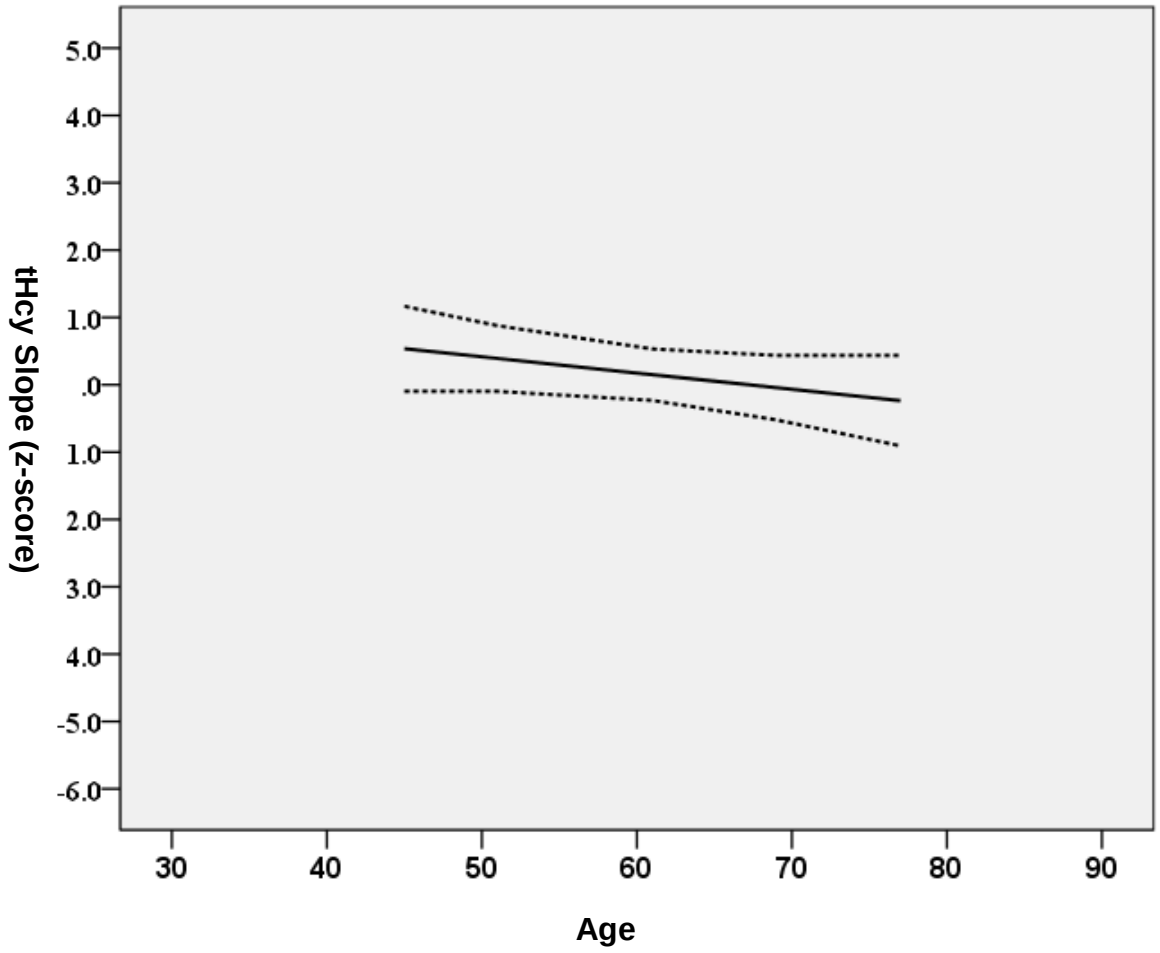


Figure obtained using Johnson-Neyman technique.

No significant moderation of slope.

Adjusted for wave 6 age, sex, education, marital status, ZDI and Framingham Scor

3.10 Summary of Results

In wave 6 cross-sectional analyses, higher Executive Function and other cognitive functions, with the exception of Working Memory, were associated with lower levels of depressive symptoms adjusted for age, sex, education, ethnicity, tHcy, and Framingham Risk Score. In CLPD analyses bidirectional associations between symptoms of depression and Executive Function were not observed. Rather, unidirectional associations were observed with higher wave 6 Executive Function predicting decreases in symptoms of depression at wave 7. These associations were also observed for wave 6 Global cognitive function and Visual-Spatial Organization and Memory function in relation to wave 7 depressive symptoms. Higher wave 6 depressive symptoms were not undirectionally associated with lowered wave 7 Executive Function and a similar pattern of non-significant results was observed for all other domains of cognitive function with the exception of Working Memory. Finally, unlike Executive Function, Scanning and Tracking was bidirectionally associated with depressive symptoms, however the inverse association of wave 6 Scanning and Tracking and wave 7 depressive symptoms was stronger than what was observed of wave 6 depressive symptoms and wave 7 Scanning and Tracking.

For conditional mediation models the direct path of age x tHcy x APOE interactions were significantly associated with changes in depressive symptoms at wave 7, however, there was no direct main effect of tHcy or indirect effect through Executive Function or other domains of cognitive functioning. However, higher Framingham Risk scores at wave 6 were directly associated with increases in wave 7 depressive symptoms and were indirectly associated with depressive symptoms through Executive

Function. Similar to Executive Function, significant indirect paths through Working Memory and Visual-Spatial Organization and Memory were also observed.

Among APOE-E4 carriers, Framingham Risk score was not indirectly associated with changes in depressive symptoms through Executive Function. However, this path was significantly different from zero through Working Memory and Global Function. Additionally APOE-E4 carriers with higher tHcy experienced marginal increases in depressive symptoms at less than 51 years of age. For APOE-E4 non-carriers, higher tHcy was also associated with increases in depressive symptoms, but these associations were delayed until after 74 years of age.

4. DISCUSSION

The purpose of this study was to explore the associations of Executive Function, homocysteine, and depressive symptoms. In the first phase of the study, we explored the cross-sectional associations of cognitive function and symptoms of depression. In the following phase, we explored the bidirectional associations of Executive Function and other domains of cognitive function and depressive symptoms. Based on the results of this phase, we explored the conditional mediation effect of homocysteine and the Framingham Risk Score (modified by age and APOE-E4 status) through Executive Function on changes in depressive symptoms. At each phase, we explored the specificity of these relationships with Executive Function as compared with a full range of cognitive domains.

4.1 Cross-Sectional Association of Symptoms of Depression and Cognitive Performance

Our cross-sectional results are consistent with those observed by Hammar & Ardal (2009). Several domains of cognitive performance were negatively associated with symptoms of depression both with and without adjustment for age, sex, education, ethnicity, and CVD-RF's (Framingham Risk Score and tHcy). This is also consistent with cross-sectional studies which have found that individuals with vascular disease and high CVD risk profiles tend to be at a higher risk for depressive symptoms and lower cognitive performance (Crichton et al., 2014; Hajjar et al., 2009; Kauhanen et al., 1999). However, few studies have examined the longitudinal associations of these variables, which has limited our ability to infer directionality, and no studies to our knowledge have examined the potential mediating role of cognitive function on changes

in symptoms as moderated by age and APOe-E4 genotype. Because the vascular depression hypothesis asserts that aging–related processes may underlie the associations of cognitive function and symptoms of depression, it is epidemiologically relevant to analyze these relationships over time in the context of an ever-aging U.S. population (Ortman et al., 2014). Moreover, the longitudinal design of this study allowed us to adjust for baseline cognitive performance and depressive symptoms, which adds to the predictive value of aging models. In the following sections, we discuss the longitudinal findings of this study as they relate to the broader base of literature, strengths and limitations, future directions, and their clinical implications.

4.2 Directional Associations of Symptoms of Depression and Cognitive Performance

Inverse unidirectional associations were observed, with several domains of cognitive performance predicting changes in symptoms of depression over the 5-year interim, however, the reverse association was largely not found. These results are consistent with the observations of Perrino et al. (2008) who assessed general cognitive function using the Color Trails Test, Part 2 (D'Elia, Satz, Uchiyama, & White, 1996), the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 2000), and the Fuld Object Memory Evaluation (Fuld, 1977). However, these results differ from those obtained by Cui, Lyness, Tu, King, and Caine (2007), who found that depression diagnosis unidirectionally predicted Trails-B and Trails B-A times, but not the reverse.

There are a few possible reasons why our results differ from those obtained by Cui, Lyness, Tu, King, and Caine (2007). Firstly, unlike the current study and Perrino et al. (2008), Cui et al. did not adjust for baseline cognitive functioning, which may have

otherwise diminished the predictive power of depression diagnosis. Second, Cui et al. defined depression diagnosis using multinomial coding (3 levels) rather than measuring symptoms continuously as was the case in the current study and in Perrino et al. This may have in turn reduced the predictive power of cognitive function in their study. Lastly, although both the current study and Cui et al. adjusted for CVD-RF's and used Executive Function measures as predictors, the current study and Perrino et al. measured Executive Function (and cognitive function more broadly) using multiple subtests to estimate performance, likely increasing the reliability of the measure. This is a particularly important point as individual measures of Executive Function have been shown to have poorer reliability compared with other measures of cognitive function (i.e., processing speed; Miyake et al., 2000), possibly because performance on tasks used to index Executive Function may depend on developing an optimal strategy which might occur in a stepwise rather than a continuous fashion, leading to an immediate increase in performance. Conversely, should one repeat the same strategy, performance may increase only slightly, stay the same or may become inappropriate, leading to an immediate drop in performance (Rabbit, Lowe, & Shilling, 2001). Using multiple measures to estimate Executive Function may better capture the diverse nature of the construct without considering all measurement variance as random error.

4.3 Homocysteine and Depressive Symptoms

Zero-order correlations showed inconsistent inverse associations between wave 6 tHcy and wave 6 and wave 7 depressive symptoms and the main effects of tHcy on depressive symptoms were largely absent in the presence of demographic and CVD-RF covariates for a pooled-age sample of community-dwelling adults. These results are

contrary to those observed in a meta-analysis by Almeida et al. (2008). However, almost all of the studies included in the meta-analysis observed differences in tHcy level by MDD/clinically significant symptom status rather than depressive symptoms measured continuously. While measuring these variables continuously increases statistical power, it is possible that the associations between tHcy and symptoms of depression are more subtle with a healthy community-dwelling, sample due to a restriction of symptom severity.

4.4 Homocysteine Moderated by Age and APOE-E4

Although the main effects of tHcy on changes in depressive symptoms were largely absent after adjusting for a range of demographic and CVD-RF's in an age-pooled sample (adjusted for three and two-way interactions), as hypothesized, the effects of tHcy on 5-year changes in symptoms were dependent upon age and APOE-E4 status. It is possible that the reason Almeida et al. (2008) observed mainly positive associations between high tHcy and depression was that their analyses were almost entirely limited to older adults. Contrary to our expectations however, positive associations between the age x tHcy interaction and changes in depressive symptoms were observed for APOE-E4 non-carriers rather than APOE-E4 carriers. It is important to note that research thus far on APOE-E4 status and depressive symptoms is limited and has been inconsistent (Niti et al., 2009; Skoog et al., 2015). This is the first study to our knowledge to explore the moderating effect of APOE-E4 in concert with tHcy for changes in depressive symptoms.

Although these findings seem contradictory, it is also important to note that associations between the interaction of age x tHcy by APOE-E4 genotype and wave 7

ZDI reflect residual change scores from wave 6 to wave 7 (adjusted for wave 6 ZDI) rather than absolute levels of depressive symptoms. This is evidenced by high levels of tHcy never emerging as a protective factor for depressive symptoms for APOE-E4 carriers, as associations of high tHcy and advancing age never approached significance for symptom reduction. However, we did observe marginally higher risk for symptom increases among younger to middle-aged adult APOE-E4 carriers. Second, we observed among APOE-E4 non-carriers that the risks associated with high tHcy for increases in depressive symptoms were not significant until after 74 years of age. Rather than APOE-E4 non-carrier status presenting as a symptom risk factor as a function of high tHcy compared with carrier status, the direction and strength of these associations may represent a compression or delay of the negative symptom effects of high tHcy for APOE-E4 non-carriers compared with carriers.

4.5 Framingham Risk Score in Relation to Depressive Symptoms and Cognitive Performance

Although associations for Framingham Risk Score were not hypothesized a priori, it is worth noting that higher Framingham Risk Score was associated with increases in depressive symptoms and lower levels of cognitive performance for the combined sample (*n* = 719) across several cognitive models. Additionally, Framingham Risk Score was a more consistent predictor of cognitive performance than either the interaction of tHcy x age x APOE-E4 or the main effect of tHcy. One possible reason for these findings is that compared with tHcy, Framingham Risk Score represents a more complete CVD-RF profile. However, there is also evidence that inclusion of tHcy level in Framingham Risk Scores may increase predictive value for CVD outcomes

(Veeranna et al., 2011). Additionally, the predictive value of tHcy for cognitive deficit and CVD may depend on advanced age (Elias et al., 2005; Rodondi et al., 2012). Though Framingham Risk Score is a well-recognized measure for assessing CVD risk and has been consistently associated with higher depressive symptoms and lower cognitive functioning in cross-sectional studies (Hajjar et al., 2009; Kaffashian et al., 2011; Kivimäki et al., 2012), other analyses have failed to find associations between Framingham/Stroke Risk Scores and subsequent increases in depressive symptoms (Cui et al., 2007; Kivimäki et al., 2012). To our knowledge, this is the first study to observe these associations across such a wide age range of adults.

4.6 Specificity of Executive Function Findings

The focus of this study was to extend the vascular depression hypothesis literature, which primarily implicates Executive Function decline as a cognitive risk factor for increases in depressive symptoms and MDD relapse. However, our results indicate that the associations between cognitive function, CVD-RF's, and symptoms of depression are more general rather than specific to Executive Function.

First, the CLPD findings of this study appeared to be similar across several domains of cognitive function, including Global cognitive performance, Visual-Spatial Organization and Memory, and Scanning and Tracking, indicating that the associations of cognitive function and depressive symptoms are more general rather than specific, consistent with the meta-analysis by Hammar & Ardal (2009). It is important to note that this may be in large part due to the composition of our Executive Function variable, which includes subtests from the Visual-Spatial Organization and Memory (i.e., Matrix Reasoning and Block Design) and Scanning and Tracking (i.e., Trails A and Trails B)

domains, which are all also contained within the Global composite. However, the Working Memory domain also contained a subtest within our measure of Executive Function (i.e., Controlled Oral Word Association) and the reverse unidirectional finding (ZDI → WM) was observed. This indicates that shared subtest makeup does not alone explain these generalized findings.

Our expanded measure of Executive Function was built upon established MSLS operationalizations of the construct which emphasized planning and set shifting (Elias et al., 2006; Robbins, Elias, Budge, Brennan, & Elias, 2005). However, several subtests across other MSLS composites which were not included in our expanded measure also require fluid ability and related demands upon aspects of Executive Function such as attention, Working Memory, and set shifting (Table 2.2), making the true distinction of our Executive Function composite and other domains unclear. Additionally, independent of overlaps with fluid ability composites in the MSLS, measures such as Matrix Reasoning and Block design have been represented both in the WAIS and the Cattell Culture Fair Tests (Matrix Reasoning) as surrogates of fluid ability (Cattell, 1949; Wechsler, 1981).

Although Executive Function and other several other domains of cognitive function largely predicted unidirectional changes in depressive symptoms, in conditional mediation analyses, Executive Function and other cognitive functions broadly were inconsistent/weak mediators of the paths from wave 6 CVD-RF's (tHcy, tHcy x age x APOE-E4 interaction, Framingham Risk Score) and changes in depressive symptoms. Although there were some exceptions to the pattern of broadly null mediation results, it is important to note the inherently increased risk for type 1 error in multiple model

mediation testing. As such, the pattern of null mediation results reflects a generalized finding similar to the CLPD despite being contrary to our mediation hypotheses.

Perhaps the most obvious reason for the generalized pattern of our cognitive models is that Executive Function is a heterogeneous construct composed of several moderately associated components (e.g., Working Memory, response inhibition, mental flexibility; Alvarez & Emory, 2006; Diamond, 2014) which fall within the conceptual umbrella of fluid ability. Previous MSLS principal component analyses have established that a single factor within the MSLS battery accounts for about 62% of performance variance with the next most explanatory factor accounting for just 14% of measurement variance (Elias et al., 2006). Furthermore, the expanded Executive Function composite utilized in this study was moderately to highly with all other domains of cognitive function including the Similarities subtest which loads significantly across all domains (Table 3.2; Elias et al., 2006). Although many validated models of cognitive ability incorporate the construct of a general cognitive ability whereby many faculties are positively associated (i.e., G-factor), meta-analyses of hundreds of factor analytic studies support the conceptual distinction between fluid (i.e., novel problem solving) and crystalized (i.e., long-term memory/overlearned) abilities (Carroll, 1993; McArdle & Hofer, 2014) despite considerable overlap. However, the distinction between general fluid ability and Executive Function is less clear and there is no established standard for what constitutes an Executive Function task versus a task of general fluid ability. Others have observed that a single factor structure represents a better model fit than a two-factor structure when applying statistical models to fluid ability subtests within the Woodcock-Johnson Tests of Cognitive Abilities (i.e., Analysis Synthesis, Concept

Formation, and Verbal Analogies) and individual tasks designed to measure aspects of Executive Function (i.e., Category Test, Trail Making Test-B, Wisconsin Card Sorting Test; Decker, Hill, & Dean, 2007). Although there is evidence for the incremental predictive power of Executive Function in maintaining activities of daily living over global cognitive ability, it is quite possible that disruption of any associated Executive/fluid ability is likely to also be associated with general cognitive decline (J. K. Johnson et al., 2007; Zheng et al., 2012). This may indicate that although Executive Function impairment is a central symptom of the depression executive dysfunction syndrome/vascular depression hypothesis, general cognitive impairment/decline represents a common symptom among those with high levels of depressive symptoms and lowered Executive Function (Alexopoulos et al., 2002).

Lastly, it is possible that lack of specificity of the associations of Executive Function and symptoms of depression compared with other domains of cognitive performance are due in part to the content of our chosen measure of depressive symptoms. The Zung Depression Inventory has been shown to be a reliable and valid measure of general depressive symptoms (Thurber, Snow, & Honts, 2002). However, there is some evidence that individuals with Executive Function deficits, and poor vascular profiles are more likely to exhibit a particular profile of depressive symptoms which includes higher psychomotor retardation, and less severe expressions of guilt, symptom insight, and agitation compared to depressed individuals without a poor vascular profile/Executive Function profile (Alexopoulos et al., 2002; Hajjar et al., 2009; Sobreiro et al., 2014). The focus of this study and of much of the literature (Hammar & Ardal, 2009) on the associations of cognitive performance with a wide aggregated array

of depressive symptoms, rather than a specific subset of symptoms associated more with vascular depression may explain why Executive Function failed to distinguish itself from other domains of cognitive function.

4.7 Mechanisms of Change

Our results relating to the Framingham Risk Score are consistent with prior cross-sectional and longitudinal analyses which have found that those with healthier cardiovascular profiles (i.e., Cardiovascular Health Score; Crichton et al., 2014; Reis et al., 2013) are likelier to have higher cognitive performance across a range of domains rather than within a specific area of functioning such as Executive Function. Additionally, although we did not observe consistent cognitive performance mediation for the associations of CVD-RF's and changes in symptoms of depression, we did observe a generalized independent predictor role of cognitive performance for changes in symptoms. As such, although many studies exploring the vascular depression hypothesis implicate the importance of Executive Function in maintaining activities of daily living and emotional regulation, it is quite possible that cerebrovascular mechanisms underlying these relationships may implicate a more generalized role of cognitive performance.

First, one of the issues in exploring the specificity of the role of Executive Function is finding a universal definition for vascular depression. Some researchers have focused on functional outcomes such as reduced Executive Function performance/treatment response (depression executive dysfunction syndrome) and others have focused on pathophysiology using neuroimaging techniques (Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008). As previously mentioned, older adults

with poor vascular health and depression tend to exhibit irregularities and decreased volume of the prefrontal cortex which is implicated in Executive Function (Jurado & Rosselli, 2007; W. D. Taylor, Aizenstein, & Alexopoulos, 2014). However, older adults with poor vascular profiles are also at higher risk for lower hippocampal/total brain volume and diffuse small vessel disease as evidenced by the presence of WMH in MRI studies (Prins et al., 2005; Royle et al., 2013; Yamawaki et al., 2015). These specific and global cerebrovascular pathologies are implicated not only in Executive Function, but decline in various domains of function including Global performance, Processing Speed, Visual-Spatial Reasoning, and Memory (Prins et al., 2005) in addition to risk for the development of late-life depression (Firbank et al., 2004; Godin et al., 2008; Herrmann, Le Masurier, & Ebmeier, 2007; van Sloten et al., 2015).

4.8 Limitations of the Current Study

The limitations of the current study should be noted: (a) Neither depressive symptoms nor cognitive function were manipulated, limiting our ability to establish causality. (b) Individuals who were not available at wave 7 had higher depressive symptoms levels and tHcy, lower cognitive performance, and higher incidence of diabetes mellitus, and previous depression diagnosis requiring treatment. This may have diminished our ability to examine the full range of the associations of CVD-RF's, cognitive performance, and depressive symptoms. However, this is a common issue in longitudinal studies and it is more likely that our results are a conservative estimate of the strength of these associations among a health sample. (c) Depressive symptoms were determined by self-report rather than by structured interview. Although this is common in depression literature, it is possible that the inclusion of a structured interview

in addition to self-report may have increased the predictive value of symptoms of depression for clinical outcomes (Uher et al., 2012). (d) We did not have a sufficiently large enough sample to determine the incremental risks associated with having two APOE-E4 alleles compared with just one APOE-E4 allele. (e) This present study was limited to a two-wave 5-year analysis as measurement of tHcy was not available before wave 6 of the MSLS. This limited our ability to study possibly non-linear associations over time. (f) Our sample was highly educated, which limited our ability to examine education as a potentially protective factor and modifier of CVD-RF's on symptoms of depression. (g) In analyzing the associations of cognitive performance and a broad array of depressive symptoms, we may have diminished our ability to determine the specificity of the associations of symptom with Executive Function. (h) Our measure of Executive Function included several subtests included in other MSLS fluid reasoning composites and is not a pure measure of Executive Function. As such, it is difficult to determine if our generalized findings are due to a true lack of differentiation between Executive Function and other measures of Fluid Reasoning.

4.9 Strengths of the Current Study

This study has several strengths: (a) To our knowledge, this is the longest duration cross-lagged panel design analysis of executive function and depressive symptoms. (b) This is the also the first study to observe the reciprocal associations of depressive symptoms and cognitive function across a wide range of cognitive abilities, allowing us to assess the relative specificity and strength of associations of Executive Function and symptoms of depression compared with other domains of cognitive function. (c) Our measure of Executive Function and other domains of cognitive

function were composed of several subtests and were validated from previous factor analyses on the MSLS battery (Elias et al., 2006). (d) The current study adjusted for several demographic and CVD-RF variables and we were able to account for previous depression diagnosis. (e) Cognitive performance and depressive symptoms were measured continuously, increasing our ability to observe subtle variations in function. (f) This is the first longitudinal analysis to consider the conditional mediation effect of homocysteine (moderated by age and APOE-E4 status) on depressive symptoms through Executive function and other domains of cognitive function. (g) Johnson-Neyman analyses conducted as part of this study allowed us to analyze the continuous moderating effect of age on the associations of homocysteine and changes in symptoms of depression rather than relying on arbitrary cut points. (h) In preliminary analysis, we were able to determine that prior depression diagnosis requiring treatment did not affect current levels of cognitive performance, extending the scope of our unidirectional CLPD findings.

4.10 Future Directions

This longitudinal study extends the vascular depression hypothesis literature in showing that those with lower cognitive performance and poor vascular profiles are at an increased risk for symptoms of depression. Additionally, we observed increased depressive symptoms among younger and middle-aged APOE-E4 carriers as a function of tHcy, while this risk was delayed until later adulthood for non-carriers. Though the results of this study and others represent a burgeoning evidence base for the validity of the vascular depression hypothesis, more research is needed to extend these findings.

First, many clinical profiles of vascular depression among older adults include gait impairment/slowing. Many studies have shown that impaired gait function/speed and falls among older adults (associated with Executive Function) may be a behavioral marker for cerebrovascular insult (Amboni, Barone, & Hausdorff, 2013; Elias, Dore, Davey, Robbins, & Elias, 2010; Pinheiro et al., 2014; Rubenstein, 2006). Although we did have behavioral gait speed tests available in wave 6 and wave 7, dual task paradigms (e.g., walking and verbal call and response) have been shown to have consistently stronger associations with cognitive function and aspects of Executive Function (i.e., attention, inhibition, working memory; Amboni et al., 2013; Holtzer, Wang, & Verghese, 2012). Additionally, a recent randomized clinical trial has shown that older adults enrolled into a 12-week aerobic exercise group experience increases in Executive Function task performance and in addition to gait speed compared with a control group (Falbo, Condello, Capranica, Forte, & Pesce, 2016). Future clinical trials need to be conducted to determine whether these increases in dual task performance as a function of aerobic exercise may also predict improvements in symptoms of depression. A study of this design would support prior trials which have found aerobic exercise to be an effective treatment for depressive symptoms among both younger and older adults (Duman, Schlesinger, Russell, & Duman, 2008; Mura & Carta, 2013; Strawbridge, Deleger, Roberts, & Kaplan, 2002).

Second, it is possible that the associations of depressive symptoms, cognitive function, and CVD-RF's are non-linear. As such, these associations may have been masked or attenuated by the relatively healthy profile of our community sample. Prior MSLS studies have shown that the cognitive risks associated with APOE-E4 genotype

are most robust in the presence of diagnosed CVD (i.e., diabetes; Dore, Elias, Robbins, Elias, & Nagy, 2009). Additionally, the associations between CVD-RF's and symptoms of depression may increase in strength as individuals approach resultant physical disability and inability to carry out activities of daily living. Although high levels of depressive symptoms increase risk for dependence and disengagement from leisure activities for older adults, it is quite possible that institutional living itself may increase risk for depressive symptoms and physical disability (McDougall et al., 2007). Longitudinal studies are needed to determine the strength and directionality of associations of institutional transition, CVD progression and symptoms of depression.

Third, the focus of this study was on the longitudinal associations of cognitive performance and a broad range of depressive symptoms. As mentioned earlier, this may have reduced our ability to determine the specificity of the relationships between subsets of symptoms and Executive Function. Although we found that Executive Function was broadly associated with symptoms of depression, exploring the bidirectional associations of Executive Function with items relating to psychomotor retardation, apathy, and loss of energy may reveal a more central role of Executive Function in the development of depressive symptoms. Another path to exploring the vascular depression subtype may be in conducting latent class analyses with subset measures of depressive symptoms and Executive Function performance. Four factor structures have been observed in both the ZDI and CES-D and it is possible that the somatic/psychomotor retardation (CES-D and ZDI) and cognitive (ZDI) elements identified by previous factor analyses (Edwards, Cheavens, Heiy, & Cukrowicz, 2010; Romera, Delgado-Cohen, Perez, Caballero, & Gilaberte, 2008) may reveal specific

associations with Executive Function. At this time, though a specific behavioral clinical profile of the vascular depression subtype has yet to be fully established (Aizenstein et al., 2016).

Lastly, the though our expanded measure of Executive Function was a significant predictor of changes in depressive symptoms, the distinctions between what constitutes an Executive Function vs. a fluid ability is unclear given their conceptual and statistical overlaps (see Section 4.6). This in turn makes the incremental value of Executive Function over other related tests of fluid ability unclear with respect to predicting changes in depressive symptoms. These distinctions may be possible to determine in future analyses after observing the strength of associations of Executive Function and depressive symptoms after adjustment for general fluid ability. It is possible that after adjusting for fluid ability, there are no unique associations between depressive symptoms and Executive Function as we have defined it in this study.

4.11 Implications for Clinical Practice

The results of this study have direct implications for clinical practice. As the percentage of U.S adults in middle and older adulthood increases, more individuals will be at risk for cognitive decline and reduction of activities of daily living through cerebrovascular insult. Our analyses in Tables 3.3 and 3.5 indicate that every 1-standard deviation decrease in Executive Function corresponds with an approximate 0.15-standard deviation higher Zung Depression Inventory score and 0.10-standard deviation increase in symptom levels over a 5-year period. Although on the individual level, these effects are relatively modest, on the population level even modest

reductions of the risks associated with depressive symptoms have important epidemiological implications.

Thus far, short-term clinical trials have been ineffective in reducing cognitive decline by way of tHcy-lowering diets with supplementation of B-vitamins among older adults, though trials of ≥ 3 years have shown to be effective in reducing stroke events (Clarke et al., 2014; Ji et al., 2013; Smith, 2008). It is possible that by later adulthood, the benefits of supplementation on cognitive health by reducing tHcy may have diminishing returns as tHcy-related cerebrovascular pathology may be cumulative over the adult lifespan. Future long-term clinical trials are needed with younger populations of adults to determine if tHcy reduction at earlier stages of life may be an effective preventative measure for reducing cognitive decline.

Although the literature for B-vitamin supplementation for depressive symptoms reduction is scarce, early evidence is promising. A Cochrane review of three randomized clinical trials (treatment 2 – 6 months duration) has shown B-vitamin supplementation among folate-deficient adults may be effective in further reducing depressive symptoms in combination with psychotropic medication (i.e., trazodone and fluoxetine). However, it is unclear whether folate supplementation may be a viable substitute for psychotropic medications or if folate deficiency is a necessary condition for symptom improvement (M. J. Taylor, Carney, Goodwin, & Geddes, 2004). It also remains to be seen whether the effects of these short-term folate supplementation trials were dependent upon reducing tHcy or CVD-RF profile. It is also entirely possible that benefits of folate supplementation on depressive symptoms reduction are a result of tHcy's conversion to S-adenosyl-methionine which regulates serotonin metabolism

(Ganguly & Alam, 2015; Refsum et al., 2004). Long-term clinical trials are needed to determine the specific mechanisms of B-vitamin supplementation on depressive symptoms.

Although supplementation trials have produced somewhat mixed results, increasing exercise and physical activity has been shown to not only be an effective preventive measure among healthy patients in maintenance of cognitive health and emotion regulation, but also as a treatment for clinical levels of cognitive impairment and symptoms of depression (Churchill et al., 2002; Mura & Carta, 2013). Higher levels of physical activity may also prevent all-cause dementia independent of APOE-E4 status (Podewils et al., 2005). Regular aerobic activity has been associated with lower tHcy in addition to improvements among several clinical markers of cerebrovascular health including lower LDL, triglycerides, blood pressure, and higher HDL, glucose sensitivity, cerebral blood flow, and levels of brain-derived neurotropic factor (Crichton et al., 2014; Duman et al., 2008; Okura et al., 2006; Yoshida et al., 2010). Lastly, inclusion of self-report items about physical activity and exercise to primary care questionnaires may increase the predictive value of Framingham Risk Scores in determining 10-year risk of CHD (Arsenault et al., 2010). Although the exact mechanisms for the cognitive/affective benefits of regular physical activity and aerobic exercise may be many-fold and unclear at this time, the possibility of reducing the social burdens associated of any or all of these risks has far-reaching public health implications.

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APPENDIX A

Zung Depression Inventory

Table A1 List of Zung Depression Inventory Items

Number	Item	Reverse-Scored
1.	I feel down-hearted and blue	
2.	Morning is when I feel the best	X
3.	I have crying spells or feel like it	
4.	I have trouble sleeping at night	
5.	I eat as much as I used to	X
6.	I still enjoy sex	X
7.	I notice that I am losing weight	
8.	I have trouble with constipation	
9.	My heart beats faster than usual	
10.	I get tired for no reason	
11.	My mind is as clear as it used to be	X
12.	I find is easy to do the things I used to	X
13.	I am restless and can’t keep still	
14	I feel hopeful about the future	X
15.	I am more irritable than usual	
16.	I find it easy to make decisions	X
17.	I feel that I am useful and needed	X
18.	My life is pretty full	X
19.	I feel that others would be better off if I were dead	
20.	I still enjoy the things I used to	X

APPENDIX B

Framingham Risk Score Weights

Table B1. Framingham Risk Score for Men

Age	Points
20-34	0
35-39	2
40-44	5
45-49	6
50-54	8
55-59	10
60-64	11
65-69	12
70-74	14
75-79	15

Total Cholesterol	Points
<160	0
160-199	1
200-239	2
240-279	3
280+	4

Systolic BP	If Untreated	If Treated
<120	-2	0
120-129	0	2
130-139	1	3
140-149	2	4
150-159	2	4
160+	3	5

Smoking Status	Points
Nonsmoker	0
Smoker	4

Diabetes Status	Points
Diabetic	0
Non-Diabetic	3

HDL	Points
60+	-2
50-59	-1
40-49	0
35-44	1
≤34	2

Point Total	10-Year Risk
≤ -3	<1%
-2	1.1%
-1	1.4%
0	1.6%
1	1.9%
2	2.3%
3	2.8%
4	3.3%
5	3.9%
6	4.7%
7	5.6%
8	6.7%
9	7.9%
10	9.4%
11	11.2%
12	13.3%
13	15.6%
14	18.4%
15	21.6%
16	25.3%
17	29.4%
18 or more	> 30%

Desk reference: National Heart Lung, and Blood Institute
http://www.ccs.ca/images/Guidelines/Tools_and_Calculators_En/Lipids_Gui_2012_FRS_BW_EN.pdf

Table B2. Framingham Risk Score for Women

Age	Points
20-34	0
35-39	2
40-44	4
45-49	5
50-54	7
55-59	8
60-64	9
65-69	10
70-74	11
75-79	12

Total Cholesterol	Points
<160	0
160-199	1
200-239	3
240-279	4
280+	5

Systolic BP	If Untreated	If Treated
<120	-3	-1
120-129	0	2
130-139	1	3
140-149	2	5
150-159	4	6
160+	5	7

Smoking Status	Points
Nonsmoker	0
Smoker	4

Diabetes Status	Points
Diabetic	0
Non-Diabetic	3

HDL	Points
60+	-2
50-59	-1
40-49	0
35-44	1
≤34	2

Point Total	10-Year Risk
≤ -3	<1%
-2	<1%
-1	1.0%
0	1.2%
1	1.5%
2	1.7%
3	2.0%
4	2.4%
5	2.8%
6	3.3%
7	3.9%
8	4.5%
9	5.3%
10	6.3%
11	7.3%
12	8.6%
13	10.0%
14	11.7%
15	13.7%
16	15.9%
17	18.5%
18	21.5%
19	24.8%
20	27.5%
21 or more	> 30%

Desk reference: National Heart Lung, and Blood Institute
http://www.ccs.ca/images/Guidelines/Tools_and_Calculators_En/Lipids_Gui_2012_FRS_BW_EN.pdf

APPENDIX C

Theoretically Relevant Covariates

Table C1. Cross-Sectional and Prospective Studies of Homocysteine and Symptoms of Depression

Authors, date	Design	Age, Gender	Covariates	Results
(Gu et al., 2012)	cross-sectional	20-90y, M/F	age, sex, BMI, exercise, education, smoking, antidepressant use, creatinine level, alcohol use, and chronic medical conditions	high Hcy predicted higher likelihood for elevated depressive symptoms
(Tiemeier et al., 2002b)	cross-sectional	≥55y, M/F	age, sex, cardiovascular disease, and functional disability	high Hcy associated with elevated depressive symptoms/Dx., but not after adjustment for functional disability and CVD
(Ng, Feng et al., 2009)	cross-sectional	≥55y, M/F	unadjusted and adjusted for age, housing size, education, social network and support, smoking, alcohol, underweight, obesity, antidepressant use, depression-inducing drugs, number of medical comorbidities, disability, unintended weight gain/loss, supplements, anemia, albumin, and creatinine	high Hcy unrelated to elevated depressive symptoms.
(Nanri et al., 2010)	cross-sectional	21-67y, M/F	age, site, job position, marital status, occupational physical activity, leisure-time physical activity, smoking and alcohol use	high Hcy associated with elevated depressive symptoms among men (trend $p = .06$), but not among women
(Almeida et al., 2008)	cross-sectional	≥65y, M	age, education, living arrangements, smoking, alcohol use, physical activity, and number of medical comorbidities	high Hcy associated with elevated depressive symptoms
(Tolmunen et al., 2004)	cross-sectional/4.0-year incident	46-64, M	month of study, ischemic heart disease, smoking, alcohol use, marital status, education, and socioeconomic status (secondary exclusion of CVD)	baseline Hcy associated with baseline and incident elevations in depressive symptoms
(Forti et al., 2010)	prospective, 3.9-year follow-up	≥65y, M/F	Exclusion control for high depressive symptoms and adjustment for education, CVD, hypertension, stroke, diabetes, chronic pulmonary disease, and cancer, ADL disability	highest homocysteine tertile associated with incident depression among women, but not in men
(Kim et al., 2008)	prospective, 2.4-year follow-up	≥65y, M/F	age, sex, education, MMSE, disability, smoking, alcohol, sedentary status, vascular risk score, serum creatinine	baseline and increase in Hcy level associated with incident depression at follow-up

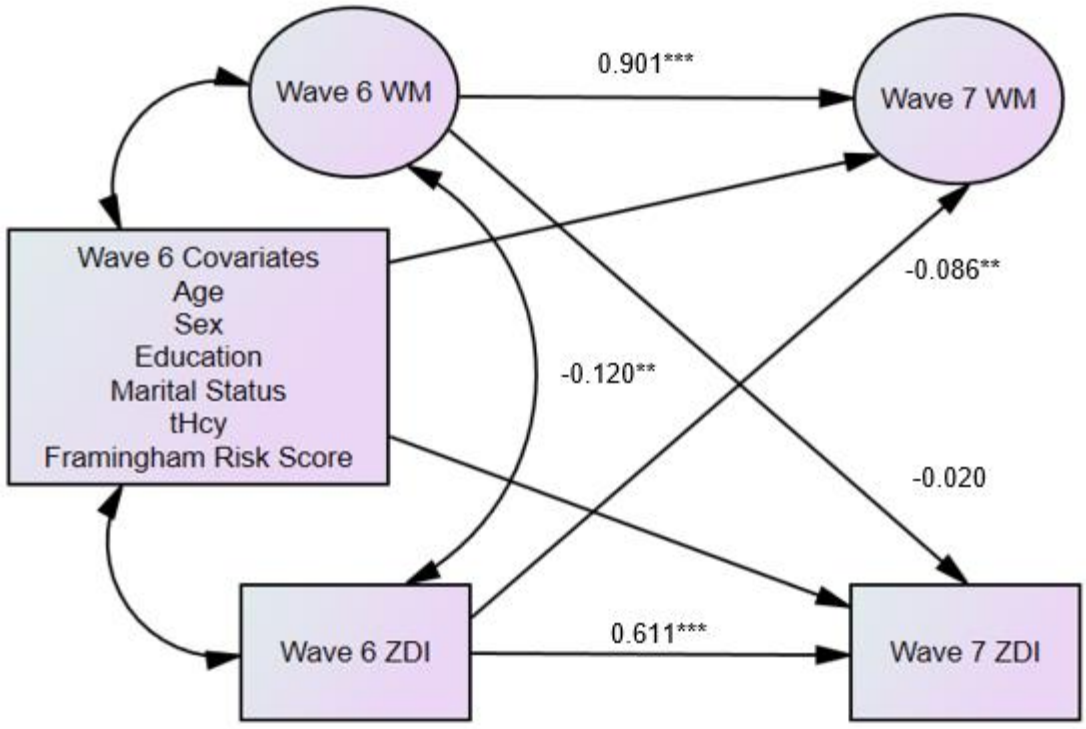
Table C2. Cross-Sectional and Prospective studies of Homocysteine and Cognitive function

Authors, date	Design	Age, Gender	Covariates	Results
(Polito et al., 2016)	cross-sectional	72-77y, M/F	age, sex, education, CVD, stroke, diabetes, high cholesterol, folic acid, systolic BP, APOE-ε4/ MTHFR, 5,10 methylenetetrahydrofolate reductase genotype	Hcy and APOE-ε4 genotype inversely associated with executive function, but not memory
(Moorthy et al., 2012)	cross-sectional	45-103y	age, sex, ethnicity, and education as well as Apo-ε4 genotype, plasma folate, plasma B-12 and B-6, kidney function, and presence of diabetes and hypertension	low plasma B-vitamins and APOE-ε4 genotype inversely associated with MMSE score and positively associated with depressive symptoms
(Elias et al., 2005)	cross-sectional	40-82	Framingham Stroke risk profile (age, systolic blood pressure, antihypertensive medication, diabetes, cigarette smoking status, cardiovascular disease, left ventricular hypertrophy, and atrial fibrillation), diabetes, creatinine, total cholesterol, BMI, alcohol intake, coffee intake, APOE-ε4 genotype, plasma B-12, B9 and B6	significant interactions between age and Hcy. Associations were found between higher Hcy among adults ≥60y and reduced global cognitive performance
(Elias et al., 2008)	cross-sectional		age, sex, education, CVD, plasma B-12 and B-6	Hcy inversely associated with global cognitive performance, MMSE, working memory, trend for similarities. Significant interaction of APOE-ε4 status on performance.
(Bonetti, Brombo, Magon, & Zuliani, 2015)	cross-sectional	≥65y, M/F	age, sex, education, stroke history, cerebral atrophy (cerebral tomography), and plasma B-12	hyperhomocysteinemia associated with highest risk for dementia Dx. and functional impairment.
(Feng, Ng, Chuah, Niti, & Kua, 2006)	cross-sectional	≥65y, M/F	age, sex, and number of years of education, cigarette smoking, alcohol consumption, BMI, total cholesterol, hypertension, diabetes, cardiovascular disease, creatinine, depressive symptoms, plasma B-9 and B-12	higher Hcy was inversely associated with processing speed and constructional ability (Block Design)
(Nurk et al., 2005)	prospective, 6-year follow-up	65-67y, M/F	sex, education, CVD, depression, baseline tHcy, and APOE-ε4 genotype	increased Hcy was associated with lower episodic memory performance
(Zylberstein et al., 2011)	Prospective, 22-year follow-up	38-60, F	age, education, BMI, cholesterol, triglycerides, systolic and diastolic BP, smoking, creatinine, and plasma B12.	highest tertile Hcy associated with higher risk for dementia and AD

APPENDIX D

Cross-Lagged Panel Analyses of other Cognitive Domains

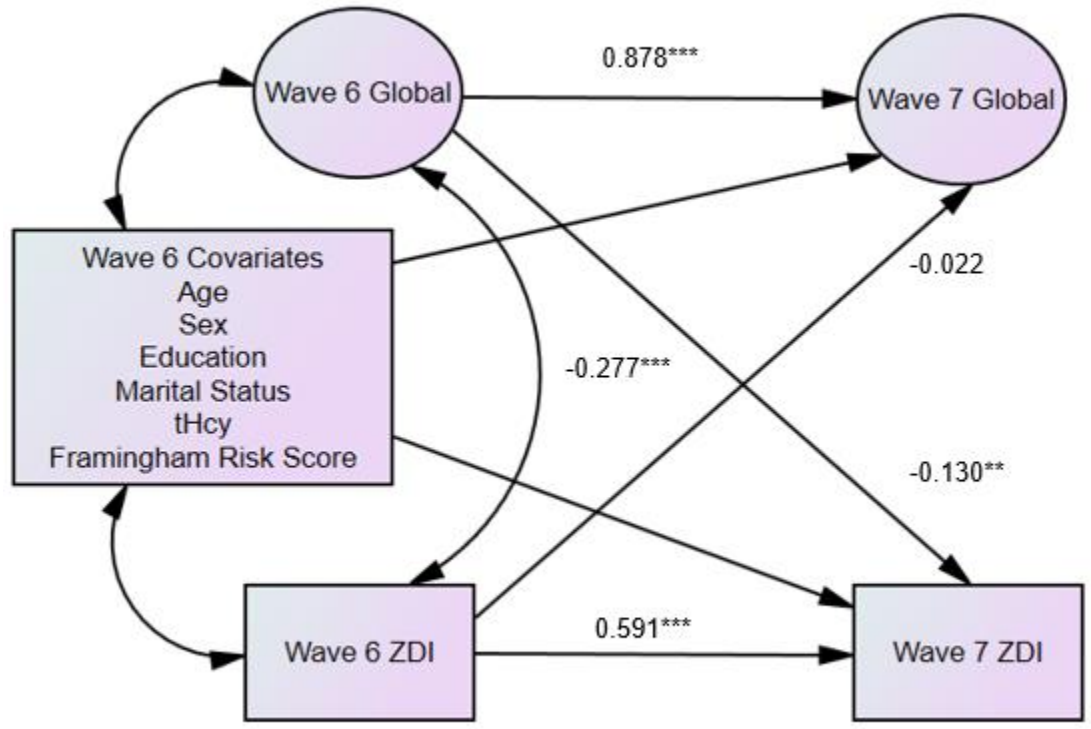
Figure D1. Cross-Lagged Panel Analysis for Working Memory



***p<.001, **p<.01, *p<.05 +p<.10
ST = Working Memory
ZDI = Zung Depression Inventory

Fit Indices
RMSE = 0.060
$\chi 2(70) = 248.316$, $p < .001$
$\chi 2/df = 3.547$
CFI = 0.954

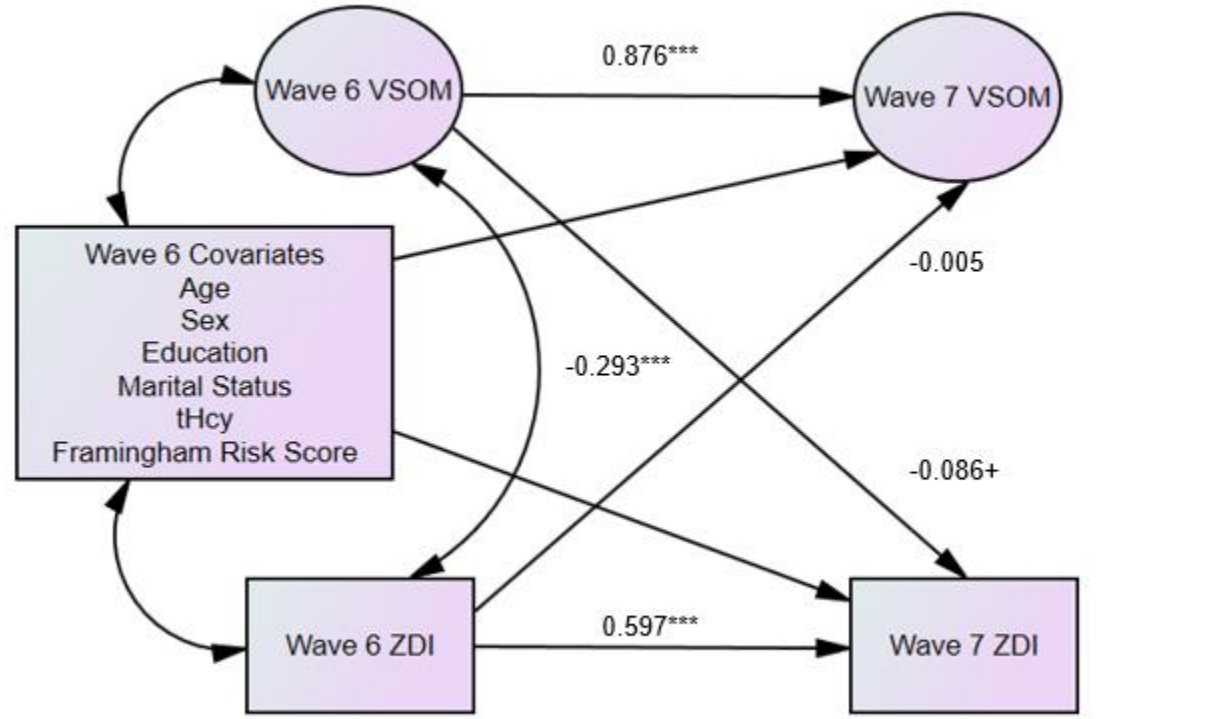
Figure D2. Cross-Lagged Panel Analysis for Global composite



***p<.001, **p<.01, *p<.05 +p<.10
ST = Scanning and Tracking
ZDI = Zung Depression Inventory

Fit Indices
RMSE = 0.077
$\chi 2(882) = 4648.440$, $p < .001$
$\chi 2/df = 5.270$
CFI = 0.816

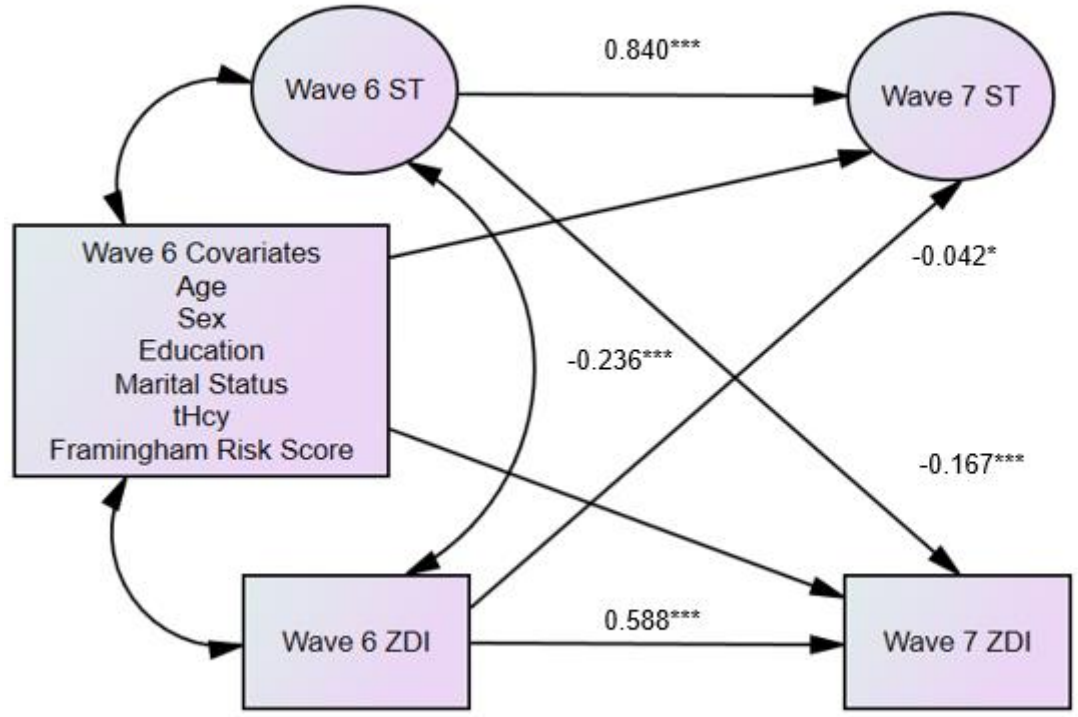
Figure D3. Cross-Lagged Panel Analysis for Visual-Spatial Organization and Memory



***p<.001, **p<.01, *p<.05 +p<.10
VSOM = Visual-Spatial Organization and Memory
ZDI = Zung Depression Inventory

Fit Indices
RMSE = 0.066
$\chi 2(138) = 573.539$, $p < .001$
$\chi 2/df = 4.156$
CFI = 0.940

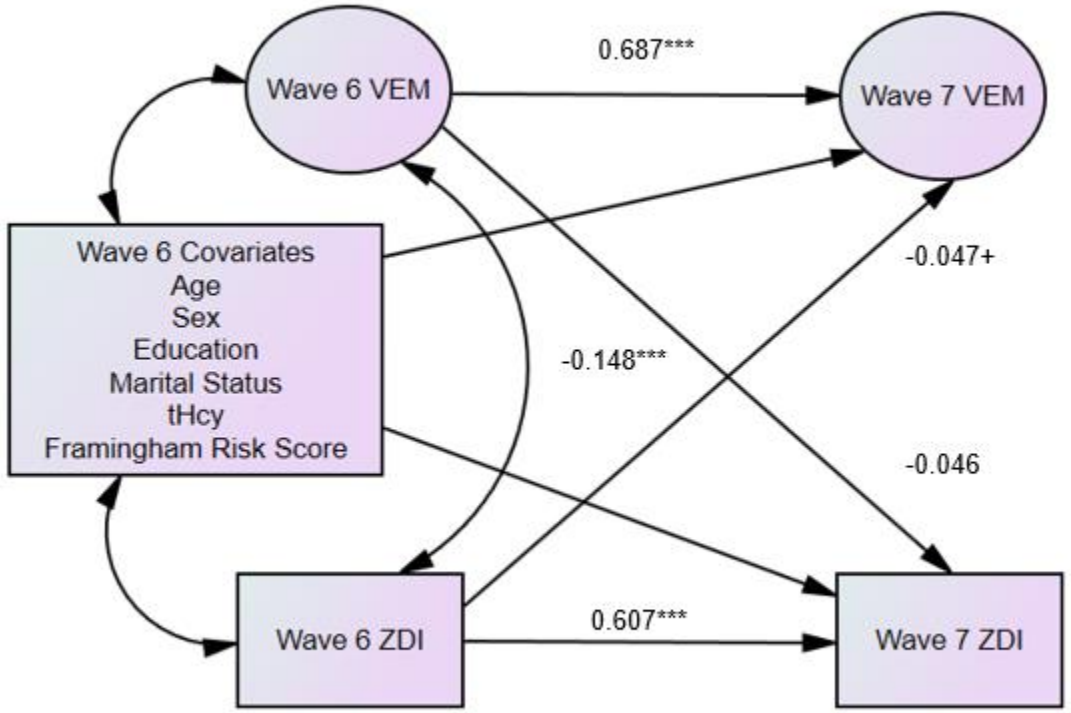
Figure D4. Cross-Lagged Panel Analysis for Scanning and Tracking



***p<.001, **p<.01, *p<.05 +p<.10
ST = Scanning and Tracking
ZDI = Zung Depression Inventory

Fit Indices
RMSE = 0.044
$\chi 2(70) = 167.777$, $p < .001$
$\chi 2/df = 2.397$
CFI = 0.984

Figure D5. Cross-Lagged Panel Analysis for Verbal Episodic Memory



***p<.001, **p<.01, *p<.05 +p<.10
VEM = Verbal Episodic Memory
ZDI = Zung Depression Inventory

Fit Indices
RMSE = 0.076
$\chi 2(42) = 216.637$, $p < .001$
$\chi 2/df = 5.158$
CFI = 0.96

BIOGRAPHY OF THE AUTHOR

Peter Dearborn was born in Boston, Massachusetts on May 4th, 1987. He was raised in Acton and then Boxborough, Massachusetts by Susan and Frank "Kenny" Dearborn. He graduated from Acton-Boxborough Regional High School in 2005. Later he attended and graduated from the University of Maine with a Bachelor's Degree in Psychology through the research intensive track in 2009. Upon graduation, he successfully completed the 2178.4-mile Appalachian Trail. After working from 2010 to 2012 as a study coordinator for the Division of Sleep Medicine at Brigham and Women's Hospital in Boston, he returned to the University of Maine for graduate study in psychology. He is currently an author on 4 publications and has received the Susan J. Hunter Excellence in Teaching Fellowship. He is currently an affiliate of the University of Maine Center on Aging and the Graduate School of Biomedical Sciences and Engineering. He is a candidate for the Doctor of Philosophy degree in Psychology from the University of Maine in December, 2017.