Synergistic Associations of Genetic, Demographic, Health, and Lifestyle Risk Factors on Neurocognitive Performance and Change in Aging

by

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ABSTRACT

Objective: Neurocognitive phenotypes observed in aging have been linked to select combinations of candidate genetic polymorphisms and modifiable risk factors. In this dissertation, I test multiple methods and approaches to examine three modifiable risk domains (i.e., demographic, health, lifestyle) and six single nucleotide polymorphisms (SNPs) (i.e., *Apolipoprotein E* [*APOE*] *Catechol-O-methyltransferase* [*COMT*; rs4680], *Brain-derived neurotrophic factor* [*BDNF*; rs6265], *Complement receptor 1* [*CR1*; rs6656401], *Clusterin* [*CLU*; rs11136000], and *Phosphatidylinositol-binding clathrin assembly protein* [*PICALM*; rs3851179]) on concurrent and longitudinal neurocognitive performance in non-demented aging and Mild Cognitive Impairment (MCI). This dissertation includes three studies. Study 1 tested SNPs, demographic, health, and lifestyle risk factors to build, compare, and validate a multi-domain risk score to predict episodic memory (EM) performance and 9-year change. Study 2 tested independent, interactive, and additive associations of two normal aging SNPs (*COMT*, *BDNF)*, and as stratified by AD-related SNP (*APOE*) on EF performance in normal aging. Study 3 examined independent and additive associations of (a) *COMT*, *BDNF*, and *APOE,* (b) *COMT* and *BDNF* as separated by *APOE* risk, and (c) as moderated by age and lifestyle activities groups on EF performance and 9-year change. **Method:** This dissertation uses data from normal aging older adults and adults classified as MCI from the Victoria Longitudinal Study (VLS): Study 1 (normal aging: $n = 568$, mean age at baseline = 68.32 years; MCI: $n = 69$, mean age at baseline = 73.36 years), Study 2 and Study 3 (normal aging: $n = 634$, mean age = 70.58 years). Study 1 was longitudinal, Study 2 was cross-sectional, and Study 3 followed an accelerated longitudinal design. I used appropriate combinations of confirmatory factor analysis, longitudinal invariance testing, parallel process latent growth models, and receiver operating characteristic curves to test

research questions in all three studies. **Results:** In Study 1, first, I observed that higher risk scores on demographic, health, and lifestyle risk factors predicted worse EM performance at age 75 years and steeper 9-year decline. Second, higher risk scores on independent and additive risk for demographic, health, lifestyle, and genetic factors predicted worse EM performance at baseline and time point 3. Third, independent risk score for demographic and health risk domains distinguished non-demented older adults from those with MCI. In Study 2, I observed that older adults with a high-risk allelic (*COMT* allelic risk + *BDNF* allelic risk) combination performed differentially worse on EF compared to their non-risk counterparts (*COMT* no allelic risk + *BDNF* no allelic risk). In Study 3, I observed that *APOE* risk carriers showed a magnified *COMT* + *BDNF* risk panel effect on EF performance at age 75 years but this effect was not present in the high lifestyle activities group. **Discussion:** I used methods and approaches to building a pre-clinical risk score with multiple domains (genetic, demographic, health, and lifestyle risk factors) that were selected to detect cognitive decline in normal aging at a point prior to dementia onset. In addition, select additive versus interactive mechanisms for cognitive aging genes may provide insight into the complex underlying mechanisms and pathways that influence neurocognitive performance in non-demented older adults. Future studies can investigate and address the applicability of our synergistic methods using select risk factors to develop theoretical concepts and identify genetic and modifiable risk factors to inform dementia prevention strategies. Such approaches also have the potential to help identify complex neurobiological and neurogenetic underpinnings of polygenic phenotypes observed in normal aging.

PREFACE

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To my parents

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CHAPTER 1: GENERAL INTRODUCTION

In recent decades, high life expectancy rates in developed countries have led to an exponential growth in dementia incidence and prevalence. Dementia researchers have shifted focus from finding a cure to identifying risk factors that may inform prevention strategies. The assumption is that targeting modifiable factors can lead to early detection of risk and thus intervention strategies that may delay cognitive decline and dementia onset in older adults (Anstey, 2014; Barnes et al., 2009; Kaffashian et al., 2013; Williams & Kemper, 2010). Currently, a variety of designs and strategies are being developed to promote optimal cognitive development and to reduce cognitive decline. For example, Anstey (2014) introduced the Cognitive Health Environment Life Course Model (CHELM). The model represents environmental, demographic, lifestyle, and genetic factors as independent variables that may influence cognitive decline. CHELM is based on the integration of six important concepts underlying cognitive development and change throughout the life course. These six interrelated concepts are differential development, intra-individual dynamics, cascades, biological mechanisms, reserve capacity, and plasticity. In addition to theoretical concepts for optimal cognitive development, reports on risk factors and dementia association studies have provided much insight. A recent review (Barnes & Yaffe, 2011) identified diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity, and physical inactivity as modifiable risk factors for the most common form of dementia, Alzheimer's disease (AD). AD, however, is multiply determined; therefore, much recent attention has focused on select combinations (composites, indices) of risk factors (Anstey, 2014; Barnes et al., 2009). In conjunction with independent risk factor identification, the development of risk indices to measure cumulative risk for at-risk adults is quickly growing. The concept of a risk index (higher score represents

increased risk) can be easily explained and justified, for both scientific and public health reasons. Risk assessment can be used to advise older adults on daily habits, dietary patterns, and health behaviors that may reduce overall risk for dementia.

Risk for dementia is also produced by non-modifiable sources, including genetic polymorphisms. Research or neurogenetics of neurodegenerative disease and aging largely focuses on candidate genetic polymorphisms and genome-wide association comparisons of AD patients and non-demented older adults. Recent research with candidate single nucleotide polymorphisms (SNPs) includes independent, interactive, and additive associations with cognitive decline (Harris & Deary, 2011; Nagel et al., 2008; Sapkota, Vergote, Westaway, Jhamandas, & Dixon, 2015; Wishart et al., 2011). Several genetic polymorphisms have been identified as risk factors for dementia. The most commonly studied, and consistently linked, genetic risk factor for AD is the *Apolipoprotein E* (*APOE*; rs7412, rs429358) polymorphism. The ε4 allele of the *APOE* gene is associated with cognitive impairment and increased risk of AD-related dementia (Brainerd, Reyna, Petersen, Smith, & Taub, 2011), whereas the *APOE* ε2 and ε3 alleles are potentially protective and neutral, respectively (Corder et al., 1994; de-Almada et al., 2012; Panza et al., 2000). Other SNPs associated with Alzheimer's dementia and normal cognitive decline include *Complement receptor 1*(*CR1*; rs6656401), *Clusterin* (*CLU*; rs11136000), and *Phosphatidylinositol-binding clathrin assembly protein* (*PICALM*; rs3851179) (Chibnik et al., 2011; Harold et al., 2009; Lambert et al., 2009). For example, *PICALM* rs3851179 allelic risk carriers (G/G, G/A) had a faster rate of episodic memory decline (Barral et al., 2012). Memory decline was observed among *CLU* allelic risk carriers (C/C, C/T) who eventually converted to Mild Cognitive Impairment (MCI) or AD (Thambisetty et al., 2013). Normal aging (NA) adults (n = 1666), from the Religious Orders Study and Rush Memory and

Aging Project, with *CR1* rs6656401 allelic risk (A/A, A/G) showed steeper decline on measures of global cognition, episodic and semantic memory, perceptual, and visuospatial speed (Chibnik et al., 2011).

Cognitive deficits observed in NA and non-demented older adults have been linked to genetic polymorphisms that modulate the effects of dopamine (DA) levels and neurotrophic factors (Bäckman, Lindenberger, Li, & Nyberg, 2010; Erickson et al., 2008). Two SNPs involving DA and neurotrophic levels are *Catechol-O-methyltransferase* (*COMT*; rs4680) and *Brain-derived neurotrophic factor* (*BDNF*; rs6265), respectively (Raz, Rodrigue, Kennedy, & Land, 2009; Savitz, Solms, & Ramesar, 2006; Starr, Fox, Harris, Deary, & Whalley, 2007; Wishart et al., 2011). *COMT* homozygotes and carriers of the risk allele (G/G, G/A) have lower levels of DA in the prefrontal cortex (Bilder, Volavka, Lachman, & Grace, 2004). In addition, *BDNF* homozygotes and carriers of the risk allele (A/A, A/G) secrete lower levels of neurotrophic factors, particularly in the hippocampus (Savitz et al., 2006). These two polymorphisms have been shown to play a crucial and magnifying role in the extent of neurocognitive deficits observed among groups of non-demented older adults (Harris & Deary, 2011; Mandelman & Grigorenko, 2012; Nagel et al., 2008; Sapkota et al., 2015).

Overview of Current Studies

These issues are further described in the next chapter. At this point, I summarize the present studies comprising this dissertation. In the following three studies, I examine risk factors associated with cognitive aging and dementia to test for differences in episodic memory and executive function (EF) performance using non-modifiable (up to six candidate genetic polymorphisms) and modifiable risk factors (from lifestyle, health, and demographic domains). In Study 1, I apply two different approaches to build a risk composite for cognitive impairment

in aging. In Study 1a, I build risk factor composites for demographic and health factors, latent constructs for lifestyle and the episodic memory factor (Anstey, Cherbuin, & Herath, 2013; Barnes et al., 2009; Jessen et al., 2011; Kivipelto et al., 2006; Reitz et al., 2010), and subsequently predict episodic memory performance and decline in (NA) older adults. In Study 1b, I categorize each risk factor based on the literature (Anstey et al., 2013; Anstey, Eramudugolla, & Dixon, 2014) to build a simple risk score of overall risk to predict episodic memory performance and decline in NA adults and validate whether this risk composite differentiates between NA and MCI groups. In Study 2, I selectively examine two genetic polymorphisms commonly tested with cognitive performance in NA, namely, *COMT* and *BDNF*. I test whether the additive or interactive approach best predicts EF performance at baseline and as modified by the more frequently associated genetic risk factor for dementia, *APOE*. In Study 3, I extend Study 2 and use the additive model for *COMT*, *BDNF*, and *APOE* to test for EF performance over 9-year period as moderated by age group and lifestyle risk factors.

Organization of the Dissertation

Chapters 1 to 3 provide the framework for the three studies in this dissertation. The present chapter, Chapter 1, is a general introduction. Chapter 2 gives a general literature review. Chapter 3 provides a general methods section pertaining to all three studies. Additional detailed introduction and method sections relevant to each study are included in the chapters for all three studies. Chapter 4 (Study 1) is titled "Multi-domain risk index for cognitive aging: Testing demographic, health, lifestyle, and genetic risk effects on episodic memory performance and change in non-demented aging and mild cognitive impairment". It explores multiple approaches to building a risk index for episodic memory performance and decline in non-demented older adults and MCI. Chapter 5 (Study 2) is titled "Synergistic associations of *Catechol-O-*

methyltransferase and *Brain-dervied neurotrophic factor* with executive function in aging are selective and modified by *Apolipoprotein E".* It tests independent, interactive, and additive associations of three genetic polymorphisms on EF performance in non-demented older adults. Study 2 has been published in a peer-reviewed journal (*Neurobiology of Aging*). Chapter 6 (Study 3), "In non-demented aging, executive function performance and change is predicted by *Apolipoprotein E*, intensified by *Catechol-O-methyltransferase* and *Brain-derived neurotrophic factor*, and moderated by age and lifestyle*"* investigates independent and additive associations of *COMT*, *BDNF*, and *APOE* allelic risk as separated by age and lifestyle risk on EF performance and change in non-demented older adults. Each study is self-contained and has its own introduction, methods, results, discussion, and reference sections. The last chapter, Chapter 7, is the general discussion and conclusion for all three studies, which summarizes all the results and discusses the potential clinical applications for the three studies.

CHAPTER 2: GENERAL LITERATURE REVIEW

Alzheimer's disease (AD) is the most prevalent cause of dementia with 60-80% of dementia cases worldwide (Barnes & Yaffe, 2011). By 2050, it has been estimated that approximately 1 in 85 adults will be living with AD, for an estimated prevalence of 106.8 million. Notably, delaying onset by one year may lead to 9 million fewer cases in 2050 (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). The principal phenotypic characteristic of AD is the gradual decline in cognitive functions. Primary clinical characteristics include memory loss, decline in global cognition, and early impairments in delayed recall, recognition, and executive function (EF). Education, family history of AD, gender, coexisting health factors (e.g., diabetes), and duration of AD have also been linked with the development and progression of AD (Muir et al., 2012; Schmidt, Wolff, von Ahsen, & Zerr, 2012).

Regarding memory problems and dementia risk, different types of facilities have been established to address rising questions and concerns from middle-aged and older adults (i.e., Alzheimer's Risk Assessment Clinic established at the Jewish General Hospital (Montreal) in 2009; see Schipper et al., 2011). Many self-assessment tools (i.e., Australian National University Alzheimer's Disease Risk Index (ANU-ADRI; Anstey, Cherbuin, & Herath, 2013)) have also been developed for researchers as well as concerned adults to examine AD risk profiles. Discovering risk and protective factors associated with memory decline will allow researchers to identify adults at a higher dementia risk. Prevention and intervention strategies for high-risk groups may reduce overall dementia incidence and delay onset.

Healthy Cognitive Aging. Currently, aging and dementia researchers are organizing theoretical concepts to identify factors associated with normal, healthy, and exceptional cognitive development and aging (Dixon & de Frias, 2014; Fiocco & Yaffe, 2010). Many

different theoretical concepts and views have been reported in the literature (e.g., cognitive reserve, see Stern, 2009). One prominent example is the Cognitive Health Environment Life Course Model (CHELM; Anstey, 2014). The CHELM provides an integrated view on enhancing and optimizing cognitive aging through risk assessment and management, as well as individualized interventions and broad policy applications. The model accounts for six theoretical concepts underlying lifespan cognitive development and change. First, differential development focuses on trajectories of change for various cognitive abilities. Differences may arise in trajectories of cognitive change due to variations in nutrition, lifestyle, gender, marital status, education, and cognitively stimulating environments. For example, previous studies have reported that married couples with greater social engagement and support perform better on cognitive tasks and show less decline with age than their unmarried counterparts (Seeman et al., 2001). Furthermore, differential cognitive performance has been associated with sex, where higher risk has been associated with poorer cognitive performance for women *APOE* ε4+ carriers than men (Altman et al., 2014; Bartrés-Faz et al., 2002). Second, intra-individual dynamics incorporates differences in cognitive performance between and within individuals. Interindividual variation are differences in performance between persons and intraindividual variation are within-person differences in performance over multiple assessments (e.g., day-to-day or year-to-year). Third, the concept of cascade seeks to describe how the decline in one system can lead to decline to another and then failure of several systems together. For example, the amyloid cascade hypothesis states that the neurofibrillary tangles, cell loss, and dementia observed in AD are a result of amyloid plaque accumulation (Hardy, 2006; Jack et al., 2010). Fourth, biological mechanisms incorporate known risk factors (i.e., age, *APOE*) to depict pathways that lead from normal brain and cognitive decline to accelerated decline and dementia.

Fifth, reserve capacity refers to the incongruous relationship between neurological damage and cognitive function. Two types of reserve capacities have been proposed in the literature (Stern, 2009), brain reserve and cognitive reserve. Brain reserve (considered a passive process) is the brain's ability to sustain a certain level of neurological damage before cognitive function becomes impaired. Cognitive reserve (considered an active process) is the brain's ability to compensate for neurological damage via recruitment of compensatory mechanisms. Reserve capacity may be influenced by multiple factors, including education, verbal ability, and brain size. Sixth, plasticity is the brain's ability to adapt to changes. These include neural reorganization and learning (Lövden, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010; Runge, Small, McFall, & Dixon, 2014). In the present study, I represent Anstey's (2014) three potential mechanisms underlying risk and protective factors that may lead to differences in episodic memory outcomes in non-demented older adults (see Figure 2-1). The figure shows the pathway from risk and protective factors to episodic memory performance outcomes and the potential mechanisms involved. I represent three potential mechanisms, namely biological mechanisms, reserve capacity, and plasticity. The three mechanisms encompass a broad range of concepts and ideas that may direct us to smaller independent processes involved. Biological mechanisms, reserve capacity, and plasticity may act as potential mechanisms underlying differential associations with risk and protective factors on cognitive (episodic memory, EF) performance and decline in aging.

Dementia Risk Indices. In the last decade, dementia research has shifted attention to developing risk indices that reflect more than one factor. This area examines the accumulation of major risk factors to quantitatively differentiate adults with high versus low risk profiles. In a recent review, Barnes & Yaffee (2011) identified seven risk factors potentially responsible for

50% of AD cases in the world. The seven risk factors were diabetes, midlife hypertension, midlife obesity, smoking, depression, lower education levels, and physical inactivity. Next, they calculated the incidence of a risk factor and its association with AD. They estimated that a 10-25% reduction in all seven risk factors could prevent up to 1.1 to 3.0 million AD cases worldwide. In the future, interventions targeting risk and protective factors may significantly change the projected increase in dementia incidence (Anstey et al., 2013). I now review the five prominent dementia risk indices reported in the literature.

First, research in the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study used risk factors associated with dementia and cognitive decline in middle aged adults to develop the dementia risk score (Kivipelto et al., 2006). Specifically, vascular risk and other risk factors were used in logistic regression models to predict the development of dementia within a 20-year period. The risk factors used in the model were age, education, gender, systolic blood pressure, body-mass index, total cholesterol, and physical activity. Next, significant beta coefficients from the model were rounded to compute whole integers and create a sum representing the total risk score. An additional risk model was examined with the inclusion of *APOE* ε4 status. Both models predicted dementia incidence 20 years later. Receiver operating characteristic (ROC) curve analyses between the two models revealed that the dementia risk score predictions were similar (Kivipelto et al., 2006).

Second, research from the Cardiovascular Health Cognition Study (CVHS) (Barnes et al., 2009) used logistic regression models to predict dementia incidence six years later and to create a late-life dementia risk index for older adults (N = 3,375; average age = 76 years). The variables comprising the index were demographic (e.g., age, years of education), cognitive function (e.g., Digit Symbol Substitution Test), medical conditions (e.g., diabetes, hypertension), physical

function (e.g., ability to prepare meals, manage money), physical performance (e.g., 15-foot walk), lifestyle factors (e.g., current alcohol consumption, body mass index), psychosocial variables (e.g., depression score on the Center for Epidemiologic Studies-Depression Scale), prescribed medication, cerebral MRI measures, carotid artery ultrasound, *APOE* ε4 status, electrocardiogram measures, and serum measures. Significant estimates for dementia were added to the logistic regression model. Beta coefficients less than or equal to 0.75 were coded as 1 and those greater than 0.75 were coded as 2 for the dementia risk index calculation. Next, adults were divided into low, moderate, and high risk for developing dementia as predicted by the risk index. More than half of the adults in the high-risk group developed dementia six years later (Barnes et al., 2009).

Third, older adults (greater than 65 years old) enrolled in a large community-based longitudinal study of Medicare recipients in northern Manhattan were used to identify vascular risk factors associated with dementia (Reitz et al., 2010). Risk factors used in the final risk score calculation were age, sex, education, ethnicity, *APOE* ε4 status, history of diabetes, hypertension, smoking, high density lipoprotein cholesterol, and waist-to-hip ratio. Beta coefficients from Cox proportional hazards models were used to determine a score for each risk factor. The sum of all risk factor scores was used as the total risk score to predict AD. Subsequently, total risk scores were categorized into quintiles (low to high risk). Higher vascular risk scores were positively correlated with an increased probability of AD risk. Specifically, adults in the fifth quintile with 28 or higher total risk score (out of 60) had a 20.5-fold greater chance of developing AD. In contrast, adults in the first quintile with less than 14 as the total risk score had 1.0-fold chance of developing AD (Reitz et al., 2010).

Fourth, older adults from the Aging, Cognition, and Dementia (AgeCoDe) study, a longitudinal study with three measurement occasions at 18-month intervals, were used to build an AD risk score (Jessen et al., 2011). The sample was randomly divided into two equal cohorts. The risk score was developed using adults in the first cohort (greater than 75 years old). Neuropsychological assessments (i.e., subjective memory, delayed verbal recall, verbal fluency, Mini-Mental State Exam [MMSE]), age, and activities of daily living were dichotomized into low and high to include in the final risk score. A composite of all the variables predicted AD with c statistic of 0.84 in the first cohort. The second cohort was used to validate the predictability of AD using the risk score developed in the first cohort. Although the c statistic was 0.79 in the second cohort, one major limitation is that neuropsychological assessments used for clinical diagnosis were included as predictors in the overall risk score. This means that the risk index is targeted at adults who already have some form of cognitive impairment (i.e., mild cognitive impairment), which limits its use in the general population (i.e., non-demented older adults).

Fifth, Anstey and colleagues (2013) conducted a systematic literature search to identify the top risk and protective factors associated with dementia and AD. There were four steps to this procedure (Anstey et al., 2013). First, a list of possible risk factors were assembled using the Alzheimer's Disease and Cognitive Decline report (Williams & Kemper, 2010) and a systematic review of the literature (see Anstey, von Sanden, Salim, & O'Kearney, 2007; Anstey, Lipnicki, & Low, 2008; Anstey, Mack, & Cherbuin, 2009; Anstey, Cherbuin, Budge, & Young, 2011). Second, risk factors significantly associated with AD were determined. Third, odds ratios were derived for all factors. Fourth, definitions were finalized for variables to be used in the ANU-ADRI. Eleven risk factors (age, sex, low education, BMI, diabetes, traumatic brain injury,

cholesterol, depressive symptoms, smoking, low social networks, pesticide exposure) and four protective factors (cognitively stimulating activities, alcohol consumption, physical activity, fish intake) were identified and used to develop the ANU-ADRI. Subsequently, the ANU-ADRI was compared with dementia risk index developed in the CAIDE study (Anstey et al., 2014; Kivipelto et al., 2006). Prior to comparison, three validation samples were examined with at least nine or more matching risk/protective factors in the ANU-ADRI. The validation samples were from (a) Cardiovascular Health Cognition Study (CVHS), (b) Rush Memory and Aging Project (MAP), and (c) Kungsholmen Project (KP). The c-statistic, which indicates the probability that the prediction outcome is better than chance, for all three validation samples were moderate for the ANU-ADRI (c-statistic > 0.70 is considered acceptable). The overall c-statistics for predicting dementia for each sample were: (a) for the CVHS the c = 0.73 (95% CI: 0.701-0.754), (b) for the MAP the c = 0.72 (95% CI: 0.678-0.764), and (c) for the KP the c = 0.65 (95% CI: 0.616-0.691). Next, the overall c-statistic for predicting dementia using the CAIDE risk index resulted in a low c-statistic (< 0.70) for all three samples: (a) for the CVHS the c = 0.57 (95% CI: 0.541-0.600), (b) for the MAP the c = 0.49 (95% CI: 0.426-0.549), and (c) for the KP the c = 0.54 (95% CI: 0.496-0.579). One explanation for low c-statistic values with the CAIDE risk score is that the CAIDE risk score was developed using risk factors from middle aged adults and the three validation samples (CVHS, MAP, KP) all consisted of older adults. This suggests that the CAIDE risk score may only be applicable to middle aged adults and not reflective of risk associated with adults in older cohorts. The ANU-ADRI, which had c-statistic closer to the acceptable range, is more tailored towards older adult risk assessment and widely available to the public. However, two important limitations remain. First, it is based on self-reports, and may not be as precise and generalizable to the general population. Second, it does not include any

biomarkers. The authors concluded that future risk index studies may benefit from the inclusion of additional risk factors (i.e., MRI measures, genetic data, history of coronary artery disease, cognitive assessments) and longitudinal datasets (Anstey et al., 2014).

In addition to these five formal risk assessment indices, there is also growing literature specifically on the effect of vascular risk factors on dementia (Debette et al., 2011). A recent study compared the Framingham stroke risk score (Elias et al., 2004), the Framingham cardiovascular risk score (D'Agostino et al., 2008), and the CAIDE dementia risk score (Kivipelto et al., 2006) in predicting 10-year cognitive decline (Kaffashian et al., 2013). Middle age adults (mean age: 55.6 years) from a British longitudinal study, Whitehall II study, were tested on reasoning, memory, verbal fluency, vocabulary, and global cognition at three occasions over a 10-year period. The Framingham stroke (mean score = 12.4) and cardiovascular (mean score = 4.5) risk scores were superior to the CAIDE dementia risk score (mean score = 6.8) in predicting global cognition. Overall, this review indicates that risk scores predicting dementia (i.e., AD) need to be improved and expanded to predict pre-clinical measures (i.e., cognitive decline) in normal aging. One goal in this dissertation is to develop a risk score that improves the accuracy of predicting non-demented cognitive performance and change.

Genetic Polymorphisms and Cognition in Aging and Dementia. The risk associated with genetic polymorphisms and cognition in normal aging older adults has been extensively reported in the literature (Harris & Deary, 2011; McFall et al., 2014; Nagel et al., 2008; Sapkota, Vergote, Westaway, Jhamandas, & Dixon, 2015; Wishart et al., 2011). To date, however, there are no reports on multifactorial risk scores including genetic polymorphism for cognitive impairment in normal aging. Current studies have explored dementia risk indices with multiple factors (Barnes et al., 2009; Jessen et al., 2011; Kivipelto et al., 2006; Reitz et al., 2010). Among

the five dementia risk indices, only three include *APOE* (ε4+) status (Barnes et al., 2009; Kivipelto et al., 2006; Reitz et al., 2010). Two recent genetic risk scores have examined the effect of cumulative genetic risk on the probability of developing dementia or changes in cognition. In the first study, a genetic risk score (GRS) was generated by adding the number of risk alleles (range: 0-16) to predict MCI to AD progression. Each allele was weighted by an odds ratio (Rodriguez-Rodriguez et al., 2013). The following SNPs were used: *ABCA7* rs3764650, *B1N1* rs744373, *CD2AP* rs9296559, *CLU* rs113600, *CR1* rs1408077, *MS4A4E* rs670139, and *PICALM* rs3851179. Adults with six or more risk alleles had a two-fold greater chance of converting to AD then those with less than six risk alleles. The second study generated a GRS using 11 SNPs (*APOE, CLU, PICALM, BIN1, CR1, ABCA7, MS4A6A, MS4A4E, CD2AP, EPHA1*, *CD33*) commonly identified with AD risk. This GRS was used to assess cognitive function in non-demented adults enrolled in the Rotterdam Study (Verhaaren et al., 2013). This GRS was primarily associated with performance on the memory domain. However, the effect was only marginal after the *APOE* SNP was removed. This implied that *APOE* risk may be playing a dominant role whereas the remaining 10 SNPs made smaller contributions towards the cumulative GRS. In addition to modifiable risk factors, it is important to take into account synergistic effects that genetic polymorphisms may have on cognitive decline (Lindenberger et al., 2008; Sapkota et al., 2015) and dementia onset (Barral et al., 2012; Thambisetty et al., 2013). I turn now to a brief review of the genetic polymorphisms examined in this dissertation research.

In the present dissertation, I examine six genetic polymorphisms associated with memory, EF, or global cognitive decline and dementia risk. The polymorphisms *APOE, CLU, CR1,* and *PICALM* are associated with episodic memory performance in normal aging and AD (Barral et al., 2012). The polymorphisms *COMT* and *BDNF* have been associated with cognitive

performance (i.e., EF) and decline in non-demented adults (Nagel et al., 2008; Papenberg et al., 2014; Sapkota et al., 2015; Wishart et al., 2011). In Study 1, I test for differences and decline in episodic memory performance. In Study 2 and 3, I test for differences and decline in EF performance. Below, I briefly review the six single nucleotide polymorphisms (SNPs) and their reported cognitive implications.

APOE. The *APOE* rs7412, rs429358 polymorphism is involved in central nervous system repair and function, and is differentiated by three alleles: ε2, ε3, and ε4. *APOE* is known to be isoform dependent with ε4 having higher risk for MCI and AD than ε3 and ε2 (Brainerd, Reyna, Petersen, Smith, & Taub, 2011; Corder et al., 1994; de-Almada et al., 2012; Dixon et al., 2014; Panza et al., 2000). The mechanism is assumed to be that the APOE lipoproteins bind to different cell-surface receptors to transport lipids and to hydrophobic amyloid-β (Aβ) peptides. This can lead to decreased synaptic function, Aβ clearance, cholesterol metabolism and mitochondrial function (Liu, Kanekiyo, Xu, & Bu, 2013). *APOE* also exerts influence on normal cognitive changes with aging through a variety of health, lifestyle, and biological factors (Runge et al., 2014; Sachs-Ericsson, Sawyer, Corsentino, Collins, & Blazer, 2010). For example, in a recent study, I observed an *APOE* effect modification on the synergistic effects of normal aging genetic polymorphisms on EF performance (Sapkota et al., 2015). Another study reported that the *APOE* genotype interacted with vascular health factors (i.e., pulse pressure) to moderate episodic memory performance (McFall et al., 2015). In both cases, the ε4+ group showed poorer EF performance with increasing normal aging genetic risk (Sapkota et al., 2015), and poorer episodic memory performance with higher pulse pressure levels (McFall et al., 2015).

CLU. CLU rs11136000 polymorphism is involved in amyloid clearance, apoptosis, brain atrophy, and disease progression in AD patients. A recent study examined *CLU* genotype and

memory performance (Thambisetty et al., 2013). The study used non-demented older adults (age = 56-86 years old) from the Baltimore Longitudinal Study, who were followed for an average of 7.5 years. Neuropsychological testing measures included six different domains: mental status, memory, world knowledge, verbal ability, verbal fluency, attention, working memory, and EF. Overall, memory decline was observed only among *CLU* risk carriers (C+) who went on to develop MCI or AD (Thambisetty et al., 2013). With regard to *CLU* and dementia, a recent study reported that healthy young adults with *CLU* allelic risk had lower white matter integrity than their counterparts (Braskie et al., 2011). The authors concluded that this presented an increased risk for developing dementia in old age.

PICALM. Recent genome-wide association studies (GWAS) have identified the *PICALM* rs541458 polymorphism as a risk factor for AD (Harold et al., 2009). *PICALM* is involved in the production of Aβ peptide and linked to the formation of amyloid plaques (Xiao et al., 2012). A recent study replicated the GWAS findings with 2816 AD and 2706 control subjects in a European population (Lambert et al., 2011). The T allele was associated with AD risk. Another study reported results with cerebrospinal fluid (CSF) Aβ-42 levels and *PICALM* allelic status (Schjeide et al., 2011). In this study, AD allelic risk (T/T) was associated with decreased CSF Aβ-42 levels and therefore increased Aβ-42 levels in the brain. To my knowledge, the only report with *PICALM* rs541458 polymorphism using T as the risk allele and cognitive functioning is by Ferencz and colleagues (2014) from the Swedish National Study on Aging and Care-Kungsholmen. They examined a genetic risk score using *PICALM* (T+)*, B1N1*, and *CLU* on cognitive performance in non-demented older adults (*n* = 2,480; age range = 60-100 years). Then they tested whether physical activity influenced the association between genetic risk score and cognitive performance. High genetic risk scores were associated with poor episodic memory

performance. Specifically, high physical activity levels mitigated the negative effects of high genetic risk score on episodic memory performance (Ferencz et al., 2014). Based on the foregoing literature, I will test *PICALM* T+ carriers as associated with risk for episodic memory decline.

CR1. The *CR1* rs6656401 polymorphism is located on chromosome 1 at the locus 1q32. CR1 is a multifunctional glycoprotein expressed on many cells including dendritic cells (Khera & Das, 2009). The protein is involved in a number of functions including regulation of the complement cascade and clearance of immune complexes. In relation to AD, CR1 acts as a receptor for the Aβ-42 peptide removal from the brain and the circulatory system (Lambert et al., 2009). Thus, the *CR1* SNP may be responsible for modifying the rate of Aβ-42 clearance in AD patients (Crehan et al., 2012). In a recent combined dataset from the Religious Orders Study and Rush Memory and Aging Project, *CR1* allelic risk (A+) carriers showed a faster decline on global cognition as measured by the MMSE compared to their non-risk counterparts (Chibnik et al., 2011).

COMT. The *COMT* rs4680 polymorphism increases COMT enzymatic activity that in turn decreases DA levels primarily in the prefrontal cortex (Chen et al., 2004; Gennatas et al., 2012). This frequently studied *COMT* polymorphism is located at codon 158 on chromosome 22q11. *COMT* homozygotes for the A allele (Met allele) have greater DA levels compared to the G allele homozygotes (Val/Val homozygotes). Thus, carriers of the G allele may be at higher risk for cognitive deficits including episodic memory and EF than homozygotes for the A allele (Nagel et al., 2008; Papenberg et al., 2014). A recent study also implicated *COMT* in predicting early cognitive impairment (Dixon et al., 2014).

BDNF. The *BDNF* rs6265 polymorphism at nucleotide 196 (G/A) is located at 11p13 and leads to a Val to Met amino acid substitution at codon 66 (Egan et al., 2003; Mandelman & Grigorenko, 2012). BDNF is a secretory protein that regulates synaptic functions including (a) synaptic plasticity and transmission, (b) long-term potentiation (LTP), and (c) synaptic growth through regulation of spine density and protein expression (Dodds et al., 2013). The protein is sorted into a regulated pathway that secretes BDNF based on neuronal activation. The *BDNF* polymorphism leads to poor dendritic trafficking and activity-dependent BDNF secretion. BDNF is mostly present in the hippocampus and prefrontal cortex. Due to its association with LTP, BDNF has also been known to play an important role in memory (i.e., verbal episodic and spatial memory) and learning (Chen et al., 2005; Dodds et al., 2013; Egan et al., 2003). However, the *BDNF* genotype has been inconsistently linked with various neurocognitive phenotypes. These include EF performance (Mandelman & Grigorenko, 2012; Nagel et al., 2008) and memory performance (Egan et al., 2003) in normal aging older adults. One recent study reported a discrepancy between *BDNF* allelic status and BDNF protein levels among 116 AD and 77 control subjects (Lee et al., 2005). In another report, there was no association between brain activation and episodic memory encoding with *BDNF* genotypes. However, *BDNF* Met carriers (A+) showed an increased activation during successful retrieval in the right hippocampus (Dodds et al., 2013), suggesting the use of possible compensatory mechanisms for this risk group.

Summary. With the global dementia epidemic, optimal cognitive aging throughout the life course has become a priority. Many risk assessment tools and facilities have been developed to address the rise in dementia incidence. Previous literature has incorporated different risk factors and developed dementia and genetic risk indices to predict both dementia risk and non-demented or normal cognitive performance and change with aging. The five notable dementia

risk scores and indices described in this literature review were (a) CAIDE risk index, (b) CVHS risk index, (c) northern Manhattan risk score, (d) AgeCoDe risk score, and (e) ANU-ADRI. Regarding genetic polymorphisms, I reviewed (a) the commonly studied *APOE* gene, (b) three polymorphisms recently identified in GWAS studies on AD risk (*CLU, CR1, PICALM*), and (c) two genetic polymorphisms associated with cognitive performance in normal aging (*COMT*, *BDNF*). On the basis of this review, I propose to examine both candidate genetic polymorphisms and modifiable risk factors (i.e., demographic, health, and lifestyle) to predict cognitive performance and change in non-demented older adults. In the investigations, I contrast different approaches to building risk indices for non-demented cognitive performance. I also compare selected methods by which synergistic associations (interactive and additive) of genetic polymorphisms differ in the level at which they predict cognitive performance in aging, as well as the extent to which these prediction patterns are modified across age and levels of other risk factors (including lifestyle activities). An overarching aim is to advance our understanding of the possible independent and interactive biological mechanisms, as they relate to modifiable risk factors, of cognitive aging. A premise is that we can better interpret the potential neurobiological mechanisms of non-demented cognitive aging by studying combinations of risk and genetic markers that may operate to moderate and modify differential cognitive trajectories in normal aging. Improved knowledge of the factors that combine or interact to predict non-demented cognitive trajectories may be useful in identifying early markers and mechanisms associated with eventual dementia outcomes.

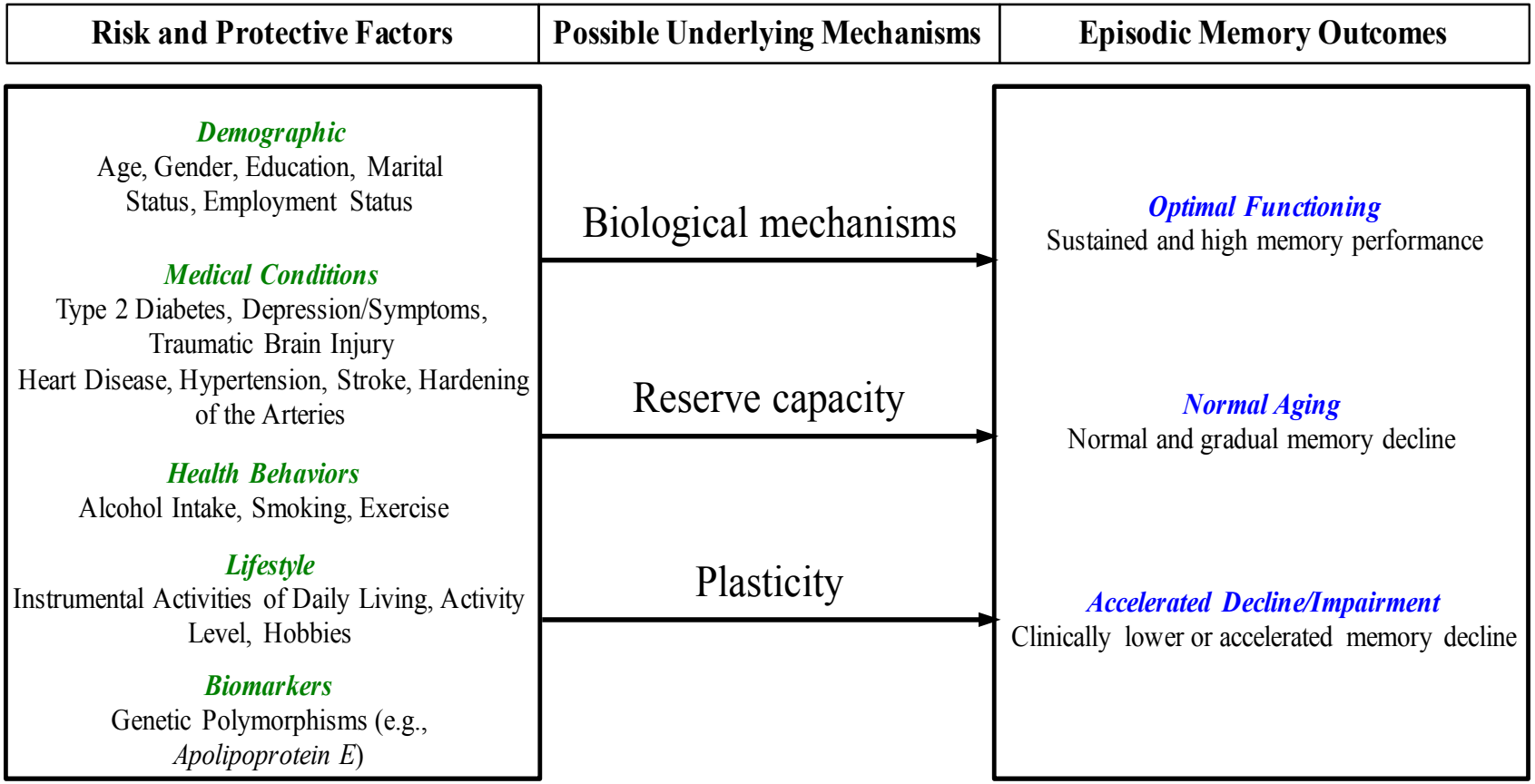

Figure 2- 1. The flow chart illustrates that biological mechanisms, reserve capacity, and plasticity may act as potential mechanisms underlying differential associations with risk and protective factors on episodic memory outcomes.

CHAPTER 3: GENERAL METHODS

The purpose of this chapter is to provide a general overview of the methods for participants, genotyping, neurocognitive measures, and risk factors, used in studies 1-3 in this dissertation. Precise detailed methodology and statistical analyses pertinent to the three studies are presented in the methods section for each one.

Participants

I use volunteer participants from the Victoria Longitudinal Study (VLS). The VLS is an ongoing large-scale and multifaceted longitudinal sequential study on biomedical, health, and neurocognitive aspects of aging (Dixon & de Frias, 2004). It was started in the late 1980s and expanded to a longitudinal sequential design with the addition of a second sample in the early 1990s and a third sample in the early 2000s. Baseline age range for all three samples is 55-85 years and all participants are re-tested at 3- to 4-year intervals. To minimize fatigue, participants are tested at four separate occasions over a period of one month for a total of 12-14 hours of testing (Dixon & de Frias, 2004; Dixon et al., 2014; Dolcos, MacDonald, Braslavsky, Camicioli, & Dixon, 2012).

All participants in the present study were community-dwelling adults and originally enrolled through advertisements. They received a small honorarium for their participation at each wave. Written informed consent was obtained from all participants. All VLS data are collected with current approval from institutional research ethics guidelines for human research. The recently collected (2009-2011) genetic sample ($N = 697$) is the source sample for this dissertation.

DNA Extraction and Genotyping. Saliva was collected according to standard procedures from Oragene-DNA stored at room temperature in the Oragene® disks until DNA

extraction. DNA was manually extracted from 0.8 ml of saliva sample mix using the manufacturer's protocol with adjusted reagent volumes. Briefly, samples were incubated for 2.5 hours at 50°C after inversion. Samples were transferred to a centrifuge tube and mixed with Oragene® purifier, incubated on ice for 10 min, then centrifuged at 15,000g for 5 min to pellet the denatured protein. The supernatant was transferred to a new tube and DNA was precipitated by adding an equal volume of 100% ethanol. The DNA pellet was washed with 70% ethanol, dried, and resuspended with 10 mM Tris, pH 8.0; 1 mM EDTA buffer. DNA was incubated at 50°C for 1 hour with occasional vortexing followed by incubation at 4°C overnight to ensure complete rehydration before quantification using a NanoDrop® ND-1000 Spectrophotometer (Wilmington, DE).

Genotyping was carried out by using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) strategy to analyze the allele status for *APOE* (determined by the combination of the SNPs rs429358 and rs7412), *BDNF* (rs6265), *COMT* (rs4680), *CLU* (rs11136000), *CR1* (rs6656401), and *PICALM* (rs541458). Briefly, SNP-containing PCR fragments were amplified in 25 ul of 1X PCR reaction mix containing 25 ng genomic DNA, 12.5 pmol of each specific primers, 6.25 nmol of each dNTP, 1.25U Taq DNA polymerase (NEB), 1.5 mM MgCl2 and 10% DMSO. Reactions were setup in 96-well plates using the QIAgility robotic system (QIAgen) and specific amplicons were amplified using a program consisting of: denaturation step at 95°C for 2 min; 40 cycles at 94°C for 30 sec, 56°C for 30 sec and 72°C for 1 min before a final extension at 72°C for 7 min.

Restriction fragment length polymorphism (RFLP) analysis was performed after digestion of the PCR amplicons with restriction enzymes (all from NEB) as follows: *APOE*: 16 hours at 37°C with HhaI; *BDNF*: 16 hours at 37°C with NlaIII; *COMT*: 16 hours at 37°C with

NlaIII; *CLU*: 4 hours at 65°C with Tsp509I; *CR1*: 7 hours at 37°C with Hpy99I; *PICALM*: 2 hours at 37°C with HpyCH4IV. RFLP analysis was then performed on a high resolution DNA screening cartridge on a QIAxcel capillary electrophoresis system (QIAgen) using the protocol OL700. The analysis was confirmed upon migration of the restriction fragments on 10 or 15% acrylamide gels for each SNP.

Neurocognitive Measures and Risk Factors

I now list the neurocognitive measures and risk factors examined throughout this dissertation. The purpose is to provide an overview of the operations used to measure each variable. First, the neurocognitive measures, which include episodic and semantic memory and executive function (EF) performance, are described. Second, modifiable (demographic, health and lifestyle) and non-modifiable (genetic polymorphisms) risk factors are presented.

Episodic and Semantic Memory Measures

Four measures of episodic (REY List A6; REY List B1; Word List Free Recall 1 and 2) and three measures of semantic (Vocabulary; Fact Recall Test 1; Fact Recall Test 2) memory were examined for the episodic and semantic memory factors.

Word List Free Recall (Word Recall). From a total of six lists, two different but comparable lists of 30 English words (i.e., five taxonomic categories for six words) (Dixon et al., 2004) were used for word recall task measuring episodic memory. There were 6 words from each of the five taxonomic categories (e.g., spices, relationships, fabrics, insects, furniture) presented on a single page. Participants were given 2 minutes to study the list and 5 minutes to write as many words as they could recall. Participants did not see the same list more than once during their three waves of testing. The total numbers of words correctly recalled from each list were used.

Rey Auditory Verbal Learning Test (REY). 15 nouns (List A) were read aloud to participants, followed by free recall (List A1). This was repeated for five trials (List A1-A5) with List A being read aloud before each free recall. Then a second interference list (List B) with 15 different nouns was read aloud, followed by free recall (List B1). Finally, participants were asked to recall the first list (List A6) (Vakil & Blachstein, 1993). The total number of nouns recalled in List A6 and List B1 were used to measure retention and free recall, respectively (McFall et al., 2015).

Vocabulary. 54 multiple-choice vocabulary questions from the Educational Testing Service kit (Ekstrom, French, Harman, & Dermen, 1976) were used to measure vocabulary or semantic memory. Participants were given 15 minutes to answer all questions. The total number of correct answers constituted the final score.

Fact Recall. Two versions of a general information test (40-items each) taken from a normed battery (Nelson & Narens, 1980) were administered. General information questions focused on a variety of topics including history, sports, entertainment, and geography (e.g., *What is the last name of the author of the book "1984"?*). The questions were in booklets and the participants had to write their answers on a blank line below the question. Both versions of the test were self-paced. The total numbers of facts correctly recalled from each version (Fact Recall 1) and (Fact Recall 2) were used.

Executive Function Measures

Two dimensions of EF (inhibition, shifting) were each measured by two standard and frequently used tests for both behavioral and clinical studies in older adults (de Frias, Dixon, & Strauss, 2006; McFall et al., 2014; McFall et al., 2013; Sapkota et al., 2015).

Hayling Sentence Completion (Hayling; Inhibition). This test (Burgess & Shallice, 1997) consists of two sections, each comprising fifteen sentences. In the first section, participants must state the last word that correctly completes the sentence. In the second section, the participants must say a word that is not at all related to the sentence. The standardized scores are based on an error score from the second section and the speed of each response from both sections, which are then combined to obtain the final score (1 = impaired to 10 = superior).

Stroop (Inhibition). This test (Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997) consists of three parts. In part A, participants are asked to name four different colors that appear as 24 dots in six different rows. In part B, the same colors appear but are printed as common words. In part C, each different color is represented as a textual representation in different colored ink. The participants are measured based on latencies. The final score is the standardized Stroop interference index ([Part C- Part A]/ Part A), with a lower index reflecting better performance.

Brixton Spatial Anticipation (Brixton; Shifting). This test (Burgess & Shallice, 1997) consists of 10 different circles; one being blue while the rest are colorless. The circles appear in a 56-page booklet. The blue colored circle shifts position with some logical pattern after each page. This test measures the mechanism of shifting by asking participants to guess where the blue colored circle will appear on the next page. The total number of incorrect guesses are measured and the final scores are calculated (1 = impaired to 10 = superior).

Color Trails (Shifting). This test (D'Elia, Satz, Uchiyama, & White, 1996) comprises two different tasks in which participants connect different attributes, such as numbered and colored circles. In the first section, participants connect numbers from 1–25 within circles that are randomly organized on a page. In the second section, they connect the numbers in order but

alternating between pink and yellow circles. Errors and latency scores are then computed to obtain the standard overall score.

Risk Factors

Demographic. The VLS personal data sheet was used to determine type and level of demographic risk score. Based on previously reported literature on demographic risk factors and cognitive performance, I included education (Springer, McIntosh, Winocur, & Grady, 2005), marital status (Seeman, Lusignolo, Albert, & Berkman, 2001), age (Bäckman et al., 2000) and gender (Bartrés-Faz et al., 2002) for this domain. Education was calculated by adding the total number of school years completed including any high school, college, graduate, vocational or technical school. Education was used as both a continuous variable and categorical variable. For the categorical variable, education greater than 14 years was coded 0 (indicating no risk), 12-14 years was coded 1 (low risk), and less than 12 years was coded 2 (high risk). For marital status, participants were asked to state whether they were (a) married, (b) single, (c) widowed, (d) divorced, or (e) separated. For the purpose of the present studies, I categorized participants into married (no risk = 0) and not married (risk = 1). For gender, participants indicated whether they were male or female. I coded male as 0 (no risk) and female as 1 (risk). Age was computed by subtracting birth year from the testing year. I used age as both continuous and categorical variable. For the categorical variable, age less than 65 years was coded 0 (no risk), 65-75 years was coded 1 (low risk), 76-85 years was coded 2 (intermediate risk), and greater than 85 years were coded 3 (high risk). All continuous measures were reversed coded to indicate higher risk with increasing score. The demographic composite was used in Study 1. It was calculated by adding the risk composites for both the categorical and continuous measures as described in Study 1. Higher scores indicated greater demographic risk.

Health. The VLS personal data sheet was used to report health conditions. In this dissertation, nine conditions were used to represent health risk contributions: diabetes (McFall et al., 2013), depression (Lichtenberg, Ross, Millis, & Manning, 1995), heart disease (Dardiotis et al., 2012), stroke (Kalaria & Ballard, 2001), hypertension (Kilander, Nyman, Boberg, Hansson, & Lithell, 1998), hardening of the arteries (Zheng et al., 2012), alcohol dependence (Hoang, Byers, Barnes, & Yaffe, 2014), tobacco dependence (Sabia et al., 2012), and any history of traumatic brain injury (Anstey, Cherbuin, & Herath, 2013). Participants were asked to self-rate each condition ranging from no (0) to yes, very serious (3). Ratings for all nine conditions were added and used as the final health risk composite score. Higher scores indicated greater health risk.

Lifestyle. The VLS Activity Lifestyle Questionnaire (VLS-ALQ) with 67-items was used to determine the level of activity for the following four domains: (a) social activity measured with 7-items, such as volunteering or visiting friends; (b) physical activity measured with 4-items, such as jogging or gardening (Bherer, Erickson, & Liu-Ambrose, 2013); (c) integrative information processing measured with 12-items, such as playing a musical instrument or household repairs; and (d) novel information processing measured with 27-items, such as completing jigsaw puzzles or reading the newspaper. The frequency of participation is rated on a 9-point scale with never (0), less than once a year (1), about once a year (2), 2 or 3 times a year (3), about once a month (4), 2 or 3 times a month (5), about once a week (6), 2 or 3 times a week (7), and daily (8). All the items were summed for each domain with higher scores representing greater frequency of activity (Hultsch, Hertzog, Small, & Dixon, 1999; Small, Dixon, McArdle, & Grimm, 2012). The lifestyle activities factor was examined in Study 1 and Study 3. In Study 1, lifestyle activities factor was computed as a latent variable and a composite factor. In Study 3,

the lifestyle activities factor was computed as a composite by adding the frequency for social, physical, integrative information processing, and novel information processing domains.

Genetic. Six SNPs were examined in Study 1: *COMT, BDNF, APOE, CLU*, *PICALM*, and *CR1*; and three SNPs in Study 2 and Study 3: *COMT, BDNF,* and *APOE*. In Study 1, all six SNPs were coded based on each allelic status: *COMT* (A/A; A/G; G/G)*, BDNF* (G/G; G/A; A/A)*, CLU* (C/C; C/T; T/T)*, PICALM* (C/C; C/T; T/T)*,* and *CR1* (G/G; G/A; A/A) was coded 0 (no risk homozygotes), 1 (heterozygotes), and 2 (risk homozygotes) for each of the three allelic contributions. *APOE* (ε2/ε2; ε2/ε3; ε2/ε4; ε3/ε3; ε3/ε4; ε4/ε4) was coded from 0 (no risk) to 4 (high risk) for each allelic status with the higher number indicating greater risk. ε2/ε4 alleles were all coded as missing based on previously reported analyses (McFall et al., 2015). In Study 2 and Study 3, *COMT* (A/A; A/G; G/G) and *BDNF* (G/G; G/A; A/A) were coded 1 (no risk homozygotes), 2 (heterozygotes), and 3 (risk homozygotes), and *APOE* was dichotomized into 1 (ε4- = no risk) and 2 (ε4+ = risk).

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CHAPTER 4: STUDY 1

Multi-domain risk index for cognitive aging: Testing demographic, health, lifestyle, and genetic risk effects on episodic memory performance and change in non-demented aging and mild cognitive impairment

Introduction

Dementia is the leading cause of disability among older adults. Dementia symptoms include decline in memory, thinking, and activities of daily living. With the population aging and increased life expectancy, dementia cases have increased exponentially with older age (Qiu, De Ronchi, & Fratiglioni, 2007). Although dementia symptoms occur primarily in old age, pre-clinical manifestations of cognitive impairment occur decades before clinical symptoms appear (Bidzan et al., 2008). With a multifactorial etiology, primary and secondary prevention of dementia or cognitive impairment in older adults is concerned with delaying its onset by identifying risk and protective factors (Qiu et al., 2007). Consistently identified non-modifiable risk factors are old age and various genetic polymorphisms (i.e., *Apolipoprotien E* [*APOE*; rs7412, rs429358]). Regarding modifiable risk factors, vascular and psychosocial factors have been examined in recent studies (Anstey, Cherbuin, & Herath, 2013; Deckers et al., 2015; Qiu et al., 2007). We can aim preventive measures to the general population by identifying adults with a combination of risk factors that potentially places them at a high risk of dementia or cognitive impairment (Olanrewaju, Clare, Barnes, & Brayne, 2015). Recent studies have developed the concept of dementia risk scores or indices, whereby high scores on multiple risk factors indicate greater risk of cognitive decline or dementia onset.

The first dementia risk index was introduced by Kivipelto and colleagues (2006) in the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study. Scores for middle-aged adults on eight risk factors linked to dementia (age, education, gender, systolic blood pressure, body mass index, total cholesterol, physical activity, *APOE*) were used to create the index. Logistic regression models were tested on 20-year follow-ups for dementia diagnosis. Beta coefficients from the model were summed to build the overall dementia risk index. The risk

index was then categorized into low risk, intermediate risk, and high-risk profiles. As expected, the probability of dementia increased from the low-risk to the high-risk profile.

Several other studies (Anstey et al., 2013; Barnes et al., 2009; Jessen et al., 2011; Reitz et al., 2010) have developed risk indices using similar risk factors assessed in two groups, usually adults with and without dementia diagnosis. A recently developed self-assessment tool, the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) calculates risk scores using both risk and protective factors. The ANU-ADRI includes eleven risk factors (age, education, gender, diabetes, depression, BMI, brain injury, smoking, alcohol intake, cholesterol, pesticide exposure) and four protective factors (physical activity, cognitive activity, social engagement, fish intake) that were identified through a systematic review of the Alzheimer's disease (AD) literature. The tool was developed for large populations of older adults at various levels of dementia risk. The goal was to inform possible broad-based prevention strategies in the future. The ANU-ADRI has the advantage of being translatable across multiple data archives and clinical settings. One corresponding limitation is that it does not include biological or genetic risk factors and markers. Incorporating unavoidable and non-modifiable risk factors (i.e., genetic markers) with modifiable risk factors may produce a more comprehensive dementia risk score (Barnes et al., 2009; Kivipelto et al., 2006; Reitz et al., 2010).

Despite advances in this area (Anstey et al., 2013; Barnes et al., 2009; Jessen et al., 2011; Kivipelto et al., 2006; Reitz et al., 2010), the inclusion of both dementia-related single nucleotide polymorphisms (SNPs) and modifiable lifestyle factors in the same dementia risk index is fairly new. To our knowledge, only *APOE* has been included in such indices, and then only as a categorical variable (ε4+ versus ε4-) (Reitz et al., 2010). *APOE* ε2 and ε3 alleles are considered to be protective or neutral and the ε4 is considered to be the risk allele (de-Almada et al., 2012;

Liu, Kanekiyo, Xu, & Bu, 2013). *APOE* is known to be isoform dependent with ε4 having higher risk for Mild Cognitive Impairment (MCI) and AD than ε3 and ε2. Typically, this research has been cross-sectional (Anstey et al., 2013) and, when longitudinal, only two time points have been reported (Barnes et al., 2009; Kivipelto et al., 2006). Several independent risk score calculation techniques were applied in the five dementia risk indices that have been reported in the literature (Anstey et al., 2013; Barnes et al., 2009; Jessen et al., 2011; Kivipelto et al., 2006; Reitz et al., 2010). These techniques include logistic regression models (Anstey et al., 2013; Kivipelto et al., 2006), point system based on logistic coefficients using forward and backward stepwise selection procedures and receiver operating characteristic curves (Barnes et al., 2009), cox proportional hazards models (Reitz et al., 2010), and sum of categorized risk factors (Jessen et al., 2011). Varying risk score calculations and the inclusion of specific risk factors makes each risk score dependent on the calculation method and risk factors examined.

We build upon the foundation of preceding dementia risk indices to develop and test an index for normal cognitive decline in aging. We focus on episodic memory, which is most commonly impaired in dementia patients and non-demented older adults. We incorporate a range of risk factors, both non-modifiable and modifiable, across a broad age span (40 years). We examine several different techniques to determine the best method to develop a risk score that would (a) accurately predict episodic memory performance and change and (b) differentiate non-demented older adults from those with MCI.

We extend and expand upon the development of risk indices for cognitive impairment and dementia in several key directions. In the first direction, we test whether the risk score predicts episodic memory performance and decline, which is considered a cardinal behavioral maker of preclinical dementia, and has not been previously reported. We also test whether the

risk score distinguishes two clinical groups (non-demented older adults versus a clinically classified MCI group). In the second direction, we estimate a latent factor for episodic memory, which accounts for limitations associated with single test approaches by estimating the shared variance in multiple standardized tests to define the latent construct rather than using single predictor outcomes.

In the third direction, we examine four genetic polymorphisms (*APOE, Clusterin* [*CLU*; rs11136000], *Complement receptor 1* [*CR1*; rs6656401], *Phosphatidylinositol-binding clathrin assembly protein* [*PICALM*; rs3851179]) associated with AD risk and cognitive decline (Barral et al., 2012; Harold et al., 2009; Jun, Naj, Beecham, & et al., 2010; Lambert et al., 2009; McFall, Wiebe, Vergote, Westaway, et al., 2015; Thambisetty et al., 2013) and two genetic polymorphisms (*Catechol-O-methyltransferase* [*COMT*; rs4680], *Brain-derived neurotrophic factor* [*BDNF*; rs6265]) associated with cognitive decline in non-demented older adults (Nagel et al., 2008; Papenberg et al., 2014; Sapkota, Vergote, Westaway, Jhamandas, & Dixon, 2015; Wishart et al., 2011). We test genetic risk with two techniques. First, we compute a standard genetic risk score, in which we add the number of risk alleles for each SNP for every individual to create (a) a risk index for 6 genes linked to cognitive changes in older adults (*APOE, CLU, CR1, PICALM, COMT, BDNF*), (b) a risk index with 4 genes associated with AD risk (*APOE, CLU, CR1, PICALM*), and (c) an independent *APOE* risk score. This standard sum of allelic risk technique has been used by several groups to specifically examine AD risk genes (*APOE*, *CLU*, *CR1*, *PICALM*) (Ferencz et al., 2014; McFall, Wiebe, Vergote, Anstey, & Dixon, 2015). It has the advantage of being independent of memory performance, simple to apply, and straightforward to interpret. Second, we compute a formative latent genetic risk factor, in which (a) all 6 genes and (b) 4 AD risk genes are included as causal indicators with two reflective

indicators, namely, episodic and semantic memory. The formative genetic risk score represents the association between genes and which then predicts the reflective factors (episodic and semantic memory) (see Figure 4-1) (Bollen, 2011). A formative score can only be calculated when the indicators are specified as predictors for the latent composite and regression coefficients are estimated to explain variances in the formative score (Kline, 2013). The individual genotypes are modeled as causal indicators, which are assumed to have perfect score reliabilities, in the model. The regression coefficients estimate the proportions of explained variances in the latent composite (Kline, 2013). Although used previously in business and economic research (Diamantopoulos & Winklhofer, 2001; Kline, 2013), it is novel in the field of cognitive aging and dementia research. We explore and test its potential value as a means to calculate a formative genetic risk score. Overall, we compare the effectiveness of these two approaches in predicting memory performance and change, and MCI discrimination. In the fourth direction, we use statistical parallel process models to analyze a longitudinal dataset measured at three time points. These models allow us to examine whether change in risk factor over 9 years predicts episodic memory performance and decline.

Research Goals

Our overarching goal is to build, compare, and validate a multi-domain risk index for cognitive impairment in aging using demographic, health, lifestyle, and genetic risk factors. These indices will be tested and compared to find the best risk index for predicting episodic memory performance and 9-year change and for differentiating between non-demented and MCI clinical status. We explore various strategies and techniques to explore our goal. Due to well-defined differences in the methods and statistical calculations employed, we divide this study into Study 1a and Study 1b.

Specifically, the methodology for Studies 1a and 1b differs in the following ways. Study 1a examines 9-year change with modifiable risk factors and uses data in its continuous form to avoid typically examined group comparisons. Notably, Study 1a uses education and age as continuous variables and a latent lifestyle risk factor, as estimated with four lifestyle indicators: social activities, physical activities, novel information processing, and integrative information processing. Study 1b follows the established criteria in the literature (Anstey et al., 2013; Barnes et al., 2009; Jessen et al., 2011; Kivipelto et al., 2006; Reitz et al., 2010) to build risk scores through categorization and group cutoff points for each modifiable risk factor (demographic, health, and lifestyle). To this already established method (Anstey et al., 2014), we add a genetic risk score component. We examine whether it enhances or changes risk score composite calculations in predicting episodic memory performance and change, and differentiating clinical statuses (i.e., non-demented versus MCI status). First, we examine a standard genetic risk score with (a) 6 genes associated with AD risk and cognitive aging, (b) 4 AD risk genes, and (c) *APOE* risk. Second, we examine a formative composite genetic risk score with (a) 6 genes associated with AD and cognitive aging and (b) 4 AD risk genes. The risk indices for both Study 1a and Study 1b use the same demographic, health, lifestyle risk predictors, and are designed to predict episodic memory performance and change. However, Study 1a only examines modifiable risk factors (demographic, health, and lifestyle) with the available data in continuous form. Study 1b examines genetic risk factors (*APOE, CLU, CR1, PICALM, COMT, BDNF*) in addition to modifiable risk factors (demographic, health, lifestyle) to examine how different genetic risk indices (AD genes versus non-AD genes) and techniques (standard versus formative) supplement or enhance the prediction ability of the index compared to only modifiable factors.

It is important to explore the different techniques employed in Studies 1a and 1b because varying methodologies can impact the same risk factors differently and lead to contradictory outcomes. With Study 1a and 1b, we not only meet our overall goal of building a multi-domain risk index but also systematically testing and comparing modifiable and non-modifiable (genetic) risk factors, independently and cumulatively to determine the best possible and most sensitive combination in terms of (a) predicting episodic memory decline and (b) differentiating between clinical statuses.

Study 1a:

We examine three research goals in Study 1a.

Research Goal 1. There are two parts to research goal 1. First, we use confirmatory factor analysis to estimate a two-factor episodic and semantic memory latent variable and a latent lifestyle risk construct. Second, we build risk factors scores for the demographic and health risk variables with a standard technique (i.e., sum of all risk variables coded from no risk to high risk) (Anstey et al., 2014).

Research Goal 2. We establish longitudinal invariance for each time-varying latent construct (i.e., episodic and semantic memory, lifestyle risk). We expect each construct to be invariant at least at the configural and metric level across all three measurement occasions.

Research Goal 3. There are two parts to research goal 3. First, we determine the best fitting latent growth model for episodic memory and lifestyle latent variables. We chose not to examine the semantic memory latent construct because previous literature shows that semantic memory does not always decline with increasing age and increased risk (McFall, Wiebe, Vergote, Westaway, et al., 2015; Nyberg et al., 2003; Small, Dixon, & McArdle, 2011). Second, we determine how episodic memory performance and change in non-demented older adults is

affected by each of the modifiable risk factors (demographic, health, and latent lifestyle) alone and cumulatively. We expect to observe that higher risk scores on all three risk factors are associated with poorer episodic memory performance and steeper decline.

Study 1b:

We examine four research goals in Study 1b.

Research Goal 1. We categorize and compute five risk factor composites (from no risk to very high risk) using prior literature (Anstey et al., 2013; Barnes et al., 2009; Jessen et al., 2011; Kivipelto et al., 2006; Reitz et al., 2010). The five components are (a) demographic, (b) lifestyle, (c) health, (d) standard genetic (6 genes, 4 AD risk genes, and *APOE*), and (e) formative genetic (6 genes and 4 AD risk genes). Only the causal indicators (6 genes and 4 AD genes) contribute towards the latent genetic risk factor and the reflective indicators (in this case episodic and semantic memory factors) do not contribute towards this risk (see Bollen, 2011). We expect to observe good model fit statistics for the 4 AD risk (*APOE, CLU, CR1, PICALM*) formative genetic model.

Research Goal 2. We determine how well the score for each risk factor at baseline and time point 3 predicts episodic memory performance and change. We examine each risk factor alone (demographic, health, lifestyle, standard genetic [6 genes, 4 AD genes, *APOE*], formative genetic [6 genes, 4 AD genes]) and different combinations of risk factor composites (demographic + health, demographic + health + lifestyle, demographic + health + lifestyle + standard genetic [6 genes, 4 AD genes, *APOE*], demographic + health + lifestyle + formative genetic [6 genes, 4 AD genes]).

Research Goal 3. We determine whether change in each risk factor score from time 1 to time 3 predicts longitudinal change in episodic memory. We apply two methods to test

longitudinal change because we want to detect any significant changes and test which would be more sensitive to predict memory performance. Specifically, we examine (a) change score for each risk factor and (b) a latent growth model of change. In both cases, our prediction is that greater change in risk score will be associated with steeper episodic memory decline.

Research Goal 4. We determine whether each of the four risk factors alone (demographic, health, lifestyle, standard genetic [6 genes, 4 AD genes, *APOE*]) or cumulatively (demographic + health, demographic + health + lifestyle, demographic + health + lifestyle + standard genetic [6 genes, 4 AD genes, *APOE*]) discriminates between NA versus MCI status. We expect all four independent risk factors to significantly discriminate NA adults from MCI adults. However, we also expect that the overall cumulative risk score will be a better predictor than any independent risk variable.

Method

Participants

All participants were community-dwelling adults and originally enrolled through advertisements in the Victoria Longitudinal Study (VLS). They received a small honorarium for their participation at each wave. Written informed consent was obtained from all participants. All VLS data are collected with current approval from institutional research ethics guidelines for human research. The recently collected (2009-2011) genetic sample ($N = 697$) is the source sample for the present study. In the present study, we used the three main VLS cohorts (Samples 1-3) as represented in the source sample. We included Sample 1: Waves 5-7, Sample 2: Waves 3-5, and Sample 3: Waves 1-3. The longitudinal period included approximately 9 years (three waves). In this study, (a) Wave 1 refers to Sample 1 (Wave 5), Sample 2 (Wave 3), and Sample 3 (Wave 1), (b) Wave 2 refers to Sample 1 (Wave 6), Sample 2 (Wave 4), and Sample 3 (Wave 2),

and (c) Wave 3 refers to Sample 1 (Wave 7), Sample 2 (Wave 5), and Sample 3 (Wave 3). The average interval between each waves were 4.7 years between Waves 1 and 2, and 4.3 years between Waves 2 and 3.

MCI Classification. Using the recently collected genetic sample, we used an objective classification system as applied independently in two consecutive longitudinal waves to create the MCI group. This classification has been applied in past VLS studies (Dixon et al., 2014; Dolcos, MacDonald, Braslavsky, Camicioli, & Dixon, 2012). All MCI participants in this study were validated in status at a second wave (i.e., that they were stable in their original classification over a 4-year period). The cognitive status classification procedure requires strict implementation of an established four-step procedure, as applied in previous VLS studies and consistent with other research and observations (Albert et al., 2011; de Frias, Dixon, & Strauss, 2009; Dixon et al., 2014; Dixon et al., 2007; Ritchie, Artero, & Touchon, 2001; Winblad et al., 2004). First, adults were stratified into two age (64-73 years and 74-95 years) and education (0-12 years or 13+ years) groups. Second, adults were placed into their matching age and education group based on four age x education group combinations. Third, the mean performances for all four groups were calculated on five cognitive domains: perceptual speed, inductive reasoning, episodic memory, verbal fluency, and semantic memory. Fourth, the scores for each participant were compared against their corresponding age x education groups. The previously established criterion to detect early signs of cognitive impairment (de Frias et al., 2009; Dixon et al., 2007; Dolcos et al., 2012; Ritchie et al., 2001) stipulated that adults who scored one standard deviation (or below) on any one or more cognitive domain were classified as MCI. This process was repeated exactly and independently at a second wave (4 years later) and only stable MCI cases for the same cognitive domains were eligible for this study. The final stable MCI group over two

consecutive waves included *n* = 69 adults (mean age = 73.36 years, gender: 56.5% female, mean education: 14.26 (3.01) years; see Table 4-1) from VLS Sample 1 (Waves 5-6) and Sample 2 (Waves 3-4) (Dixon et al., 2014).

Normal Aging Classification. For the normal aging group, we applied the following exclusionary criteria to the main source sample (*N* = 697): (a) diagnosis or history of dementia, (b) anti-psychotic medication, (c) Mini Mental State Exam Scores < 24, (d) insulin-controlled diabetes, (e) uncontrolled hypertension, and (f) history of serious head injury (e.g., hospitalized) in Sample 1 (Wave 6), Sample 2 (Wave 4), and Sample 3 (Wave 1). Next, we excluded any individuals who were classified as stable MCI over a 4-year period. Accordingly, we included *n* = 562 normal aging older adults (mean age = 68.32 years, gender: 67.4% female, mean education: 15.40 (2.94) years) at baseline (see Table 4-1).

DNA Extraction and Genotyping. Saliva was collected according to standard procedures from Oragene-DNA stored at room temperature in the Oragene® disks until DNA extraction. DNA was manually extracted from 0.8 ml of saliva sample mix using the manufacturer's protocol with adjusted reagent volumes. Specific details outlining the genotyping procedure are provided in Chapter 3 (General Methods).

Based on previous literature, we test the allelic groups as risk homozygotes, heterozygotes, and no risk homozygotes for all six SNPs: *APOE* (risk: ε4/ε4, ε4/ε3, heterozygotes: ε3/ε3, no risk: ε2/ε2, ε2/ε3) (McFall et al., 2015); *COMT* (risk: G/G, heterozygotes: G/A, no risk: A/A); *BDNF* (risk: A/A, heterozygotes: A/G, no risk: G/G); *CR1* (risk: A/A, heterozygotes: A/G, no risk: G/G); *PICALM* (risk: T/T, heterozygotes: T/C, no risk: C/C) (Ferencz et al., 2014); and *CLU* (risk: C/C, heterozygotes: C/T, no risk: T/T). Adults with

APOE ε2/ε4 allelic combination were deleted (McFall, Wiebe, Vergote, Anstey, et al., 2015; Sapkota et al., 2015).

Episodic Memory. CFA models at all three time points were represented by two-factor episodic (REY List A6; REY List B1; Word List Free Recall) and semantic (Vocabulary; Fact Recall Test 1; Fact Recall Test 2) memory models. Although we include semantic memory in the two-factor model, we only examine the episodic memory domain.

Word List Free Recall (Word Recall). From a total of six lists, two different but comparable lists of 30 English words (i.e., five taxonomic categories for six words) (Dixon et al., 2004) were used for measuring episodic memory. The total numbers of words correctly recalled from each list was used as the final score for list 1 and list 2.

Rey Auditory Verbal Learning Test (REY). 15 nouns (List A) are read aloud to participants, followed by free recall for five trails (List A1-A5). Then a second interference list (List B) with 15 different nouns is read aloud, followed by free recall (List B1). Finally, participants had to recall the first list (List A6) (Vakil & Blachstein, 1993). The total number of nouns recalled in List A6 and List B1 were used to measure retention and free recall, respectively (McFall, Wiebe, Vergote, Westaway, et al., 2015)

Vocabulary. The total number of correct answers from the Educational Testing Service kit (Ekstrom, French, Harman, & Dermen, 1976) with 54 multiple-choice vocabulary questions was obtained for a final score.

Fact Recall. Two versions of general information (e.g., arts) test (40-items each) taken from a normed battery (Nelson & Narens, 1980) were administered. The total numbers of facts correctly recalled from each version (Fact Recall 1) and (Fact Recall 2) were used.

Risk Factors. Below we list indicators from the VLS database used to measure each risk factor. In Table 4-2 we list relevant literature sources for categorizing groups and direction for variables as risk. All measures are coded with higher scores representing greater risk based on literature.

Demographic. The VLS personal data inventory was used to determine type and level of demographic risk. Based on previously reported literature on demographic risk factors and cognitive performance, we included education (Springer, McIntosh, Winocur, & Grady, 2005), marital status (Seeman, Lusignolo, Albert, & Berkman, 2001), age (Bäckman et al., 2000) and gender (Bartres-Faz et al., 2002) for this domain. Education was calculated by adding the total number of school years completed including any high school, college, graduate, vocational or technical school. We categorized participants into married (no risk = 0) and not married (risk = 1). For gender, participants indicated whether they were male or female. We coded male as 0 (no risk) and female as 1 (risk). Age was coded in years.

Health. The VLS personal data inventory was used to report health conditions. Nine conditions were used to represent health risk contributions: diabetes (McFall et al., 2013), depression (Lichtenberg, Ross, Millis, & Manning, 1995), heart disease (Dardiotis et al., 2012), stroke (Kalaria & Ballard, 2001), high blood pressure (Kilander, Nyman, Boberg, Hansson, & Lithell, 1998), hardening of the arteries (Zheng et al., 2012), alcohol dependence (Hoang, Byers, Barnes, & Yaffe, 2014), tobacco dependence (Sabia et al., 2012), and any history of traumatic brain injury (Anstey et al., 2013). Participants were asked to self-rate each condition ranging from no (0) to yes, very serious (3). Rating on all nine conditions were summed and used as the final health risk composite score where higher scores indicated greater health risk.

Lifestyle. The VLS Activity Lifestyle Questionnaire (VLS-ALQ) with 67-items was used to determine the level of activity for the following four domains: (a) social activity measured with 7-items, such as volunteering or visiting friends; (b) physical activity measured with 4-items, such as jogging or gardening (Bherer, Erickson, & Liu-Ambrose, 2013); (c) integrative information processing measured with 12-items, such as playing a musical instrument or household repairs; and (d) novel information processing measured with 27-items, such as completing jigsaw puzzles or reading the newspaper. The frequency of participation is rated on a 9-point scale with never (0), less than once a year (1), about once a year (2), 2 or 3 times a year (3), about once a month (4), 2 or 3 times a month (5), about once a week (6), 2 or 3 times a week (7), and daily (8). All the items were summed for each domain with higher scores representing greater frequency of activity (Hultsch, Hertzog, Small, & Dixon, 1999; Small, Dixon, McArdle, & Grimm, 2012).

Genetic. All six SNPs were coded based on each allelic status: *COMT* (A/A; A/G; G/G), *BDNF* (G/G; G/A; A/A), *CLU* (C/C; C/T; T/T), *PICALM* (C/C; C/T; T/T), and *CR1* (G/G; G/A; A/A) was coded 0 (no risk homozygotes), 1 (heterozygotes), and 2 (risk homozygotes) for each of the three allelic status. *APOE* (ε2/ε2; ε2/ε3; ε2/ε4; ε3/ε3; ε3/ε4; ε4/ε4) was coded from 0 (no risk) to 5 (high risk) for each allelic status with higher number indicating greater risk. ε2/ε4 alleles were all coded as missing based on previously reported analyses (McFall, Wiebe, Vergote, Westaway, et al., 2015).

Study 1a

Statistical Analysis

Structural equation modeling (SEM) was used to analyze all research goals with Mplus 7 (Muthén & Muthén, 1998-2015). Descriptive statistics were calculated using SPSS 22 for Windows (SPSS Inc., Chicago, IL, USA) (see Table 4-1, 4-3 4-4). Any missing predictor values were estimated using multiple imputations in Mplus 7. Total of 50 imputations were generated and pooled for analyses (Enders, 2011; McFall, Wiebe, Vergote, Westaway, et al., 2015; Muthén & Muthén, 1998-2015). The three research goals were analyzed as follows:

Research Goal 1. We created risk composites or latent factors for all variables and the episodic and semantic memory domain. First, we used confirmatory factor analysis (CFA) models to examine loadings of all manifest variables for two-factor episodic (REY List A6, REY List B1, and Word Recall List 1 and Word Recall List 2) and semantic (Fact Recall 1, Fact Recall 2, and Vocabulary) memory construct and the lifestyle risk construct. The best CFA model was determined separately for all three measurement occasions. CFA models were tested at each of the three waves for a total of three models for the lifestyle risk and three models for the two-factor episodic and semantic memory. Each model fit was determined by examining several fit statistics. The chi-square test of model fit using the -2 log-likelihood (-2LL; $\chi^2; p >$ .05) allows for an overall indication of good model fit. Additional absolute/comparative fit indices were also examined to determine a good model fit to the data (Kline, 2011) with the root mean square error of approximation (RMSEA $\leq$ .05), comparative fit index (CFI $\geq$ .95), and the standardized root mean square residual (SRMR $\leq$ .08). Second, we built a standard risk composite for the demographic and health factor with four demographic and nine health

variables with simple addition. We note that age and education were included as continuous variables in the demographic composite.

Research Goal 2. We established longitudinal invariance from Time 1-3 (~9 years) for the best-fitting two factor episodic and semantic memory and the lifestyle model. We tested four levels of invariance for the lifestyle risk factor and the episodic and semantic memory factor. First, we tested configural invariance by setting the factor structure to be equal across all three time points. Second, metric invariance was established by allowing the factor loadings to be equal across all three occasions. Third, scalar invariance fixed intercepts to be equal at all three time points. Fourth, residual invariance set the residual variances to be equal at all three time points. A total of 12 longitudinal invariance models were tested. We considered each successive level of invariance and partial invariance obtained. The best-fit model with at least metric level invariance was used in the final risk score composite. Next, we computed factor scores for all three latent constructs (episodic memory, semantic memory, and lifestyle risk). Subsequently, multiple imputations were performed at this step to take into account any missing predictor values. As is the standard procedure in the VLS (McFall, Wiebe, Vergote, Westaway, et al., 2015), 50 datasets were imputed and pooled to analyze in all subsequent models.

Research Goal 3. Using Mplus 7 to compute a latent growth model, we examined the effect of time-varying lifestyle risk factors, and the health and demographic risk composites, on the episodic memory factor. Thus, parallel process models were appropriate for these analyses, as they permit assessment of differences in change for the predictors on episodic memory performance. Age was centered at 75 years in all the analyses. This is important because we want to identify any change in the predictor that may affect interindividual differences in intraindividual variability for episodic memory. Factor scores were computed for the lifestyle

risk factor and the episodic memory factor. The best latent growth model was determined for the episodic and lifestyle constructs. By using factor scores, we were able to use a simplified model without all the indicators. This avoided any problems with model non-convergence in Mplus. In the parallel process model, episodic memory intercept and slope were regressed on all three risk factors. First, episodic memory intercept was regressed on lifestyle intercept, health, and demographic risk composite. Second, episodic memory slope was regressed on lifestyle intercept and slope, health and demographic risk composite.

Results

Below we report results for each research goal.

Research Goal 1. The two-factor episodic and semantic memory (AIC = 1549.42; BIC = 155566.36; $\chi^2(df)$ = 4.79 (2), p = .009; *RMSEA* (90% CI) = .050 (.000-.109); CFI = 0.985; SRMR = 0.019) and lifestyle risk construct (AIC = 19950.74; BIC = 20054.69; $\chi^2(df)$ = 43.85 (11), $p < .001$; *RMSEA* (90% CI) = .073 (.051-.096); CFI = 0.974; SRMR = 0.038) provided good or adequate fit to the data at baseline. For subsequent time points two and three, we obtained good or adequate fit for both constructs. The model fit indices are listed in Table 4-5.

Research Goal 2. We obtained longitudinal invariance across all three time points at the configural, metric, and partial scalar level for latent factors representing episodic memory (AIC = 27334.71; BIC = 27531.42; $\chi^2(df)$ = 155.76 (47), $p < .001$; *RMSEA* (90% CI) = .064 (.053-.075); *CFI* = .959; *SRMR* = .058), semantic memory (AIC = 26642.85; BIC = 26786.14; $\chi^2(df)$ = 116.91 (21), $p < .001$; *RMSEA* (90% CI) = .090 (.074-.106); *CFI* = .976; *SRMR* = .057), and lifestyle factors (AIC = 38156.49; BIC = 38343.20; $\chi^2(df)$ = 103.46 (47), $p < .001$; *RMSEA* (90% CI) = .046 (.034-.058); *CFI* = .984; *SRMR* = .040) (see Table 4-6). To obtain partial scalar longitudinal invariance, the intercepts for social activity, word recall list 2, and vocabulary were

constrained to be equal across all three points for the lifestyle, episodic memory, and semantic memory factors, respectively. Since we did not obtain full scalar invariance, we did not test for residual invariance.

Research Goal 3. We determined how each latent factor changed across time by testing latent growth models for the episodic memory and lifestyle constructs. We used factor scores for each construct and age at each wave as the metric of change. First, for lifestyle, the best fit was obtained with the random intercept, random slope model (-2LL = 1573.37; AIC = 1589.37; BIC = 1624.11) (see Table 4-7). This means that the lifestyle risk factor score is different between older adults in these groups and the frequency of lifestyle activities is changing across age. Second, for episodic memory, the best fit was obtained with the random intercept, random slope model (-2LL = 1119.49; AIC = 1135.48.37; BIC = 1170.22). This means that the older adults showed interindividual differences and intraindividual change across age on episodic memory.

Next, we tested the lifestyle latent risk factor and the demographic and health risk composite in a parallel process model for predicting episodic memory performance at age 75 and 9-year decline. Lifestyle risk intercept, health risk composite and demographic risk composite significantly predicted episodic memory intercept. Specifically, higher risk on lifestyle intercept (β = -0.272; SE = 0.055; $p < .001$), health (β = -0.061; SE = 0.027; p =.024), and demographic risk (β = -0.034; SE = 0.016; p = .034) were associated with worse episodic memory performance at the centering age 75 (see Table 4-8). Lifestyle slope, health, and demographic composites significantly predicted 9-year episodic memory decline. Specifically, higher risk on lifestyle slope (β = -0.448; SE = 0.150; p = .003), health (β = -0.002; SE = 0.001; p =.003), and demographic risk (β = -0.001; SE = 0.001; p = .034) were associated with steeper 9-year episodic memory decline (see Table 4-8).

Predicted growth curves based on the parallel process models are graphed for demographic risk (see Figure 4-2), health risk (see Figure 4-3), and lifestyle risk (see Figure 4-4) as they predict episodic memory performance at age 75 and 9-year decline. All three risk factors in non-demented older adults predicted poor episodic memory performance at 75 years old and steeper 9-year decline with higher risk scores. As expected, the predicted growth curves for cumulative effect of high demographic + health risk and high demographic + health + lifestyle risk showed poor episodic memory performance and steep 9-year decline. Graphically, synergistic effects of demographic and health risk appeared more deleterious on episodic memory performance and change than demographic or health risk alone. Similarly, the cumulative risk of demographic, health, and lifestyle had the worst episodic memory performance and decline compared to a high score on each risk factor alone. The cumulative effects of demographic + health risk and demographic + health + lifestyle risk are represented in Figures 4-5 and 4-6, respectively.

Discussion

Our overall goal in Study 1a was to build a multi-domain risk index using relatively modifiable demographic, health, and lifestyle risk factors to predict episodic memory performance and change in non-demented older adults over 9 years. The technique for building the general risk score was to use all of the available raw data for each of the predictors in its original form. In this way, the combined risk score retained and reflected the distinct properties for each risk factor. Prior reports have examined similar modifiable and non-modifiable risk factors using a categorical approach to build their risk scores (Anstey et al., 2014). Three key findings of the present study are as follows. First, we estimated a two-factor episodic and semantic memory CFA model, and a one-factor latent lifestyle risk factor. Each latent factor was

invariant across time at the configural, metric, and partial scalar invariance level. Second, as expected higher risk scores predicted worse episodic memory performance at age 75 years and steeper 9-year decline for all three risk factors (demographic, health, lifestyle) in our random intercept and random slope growth model. Third, we observed that the synergistic effect of high risk score (demographic + health and demographic + health + lifestyle) resulted in increased spreading or "fanning" of slope effect on episodic memory performance and 9-year change than a high score on independent risk factors. We discuss each point in turn.

First, we established a two-factor model for declarative memory as represented by episodic and semantic memory factors and a one-factor model for lifestyle. The two-factor episodic and semantic memory model best represented the data at all three waves (see Table 4-5). Our result confirms previous findings that have reported a similar model for the declarative memory structure (Eichenbaum, 1997; McFall, Wiebe, Vergote, Westaway, et al., 2015), whereby episodic and semantic memory are related but stand as two separate domains at the latent variable level. This may partially explain the differential results between the two factors in older adult declarative memory performance (Nyberg, Lövden, Riklund, Lindenberger, & Bäckman, 2012; Nyberg et al., 2003). For the present analyses, we tested the episodic memory factor because it has been shown to decline with increasing age (Salthouse, 2009) and differentially so in the presence of risk factors (Anstey et al., 2014). The lifestyle indicators (social activities, physical activities, integrative information processing, novel information processing) were best represented in a one-factor model. Our estimated latent lifestyle factor allowed us to study the shared variance between all four observed lifestyle indicators in one underlying construct. For both models, we established longitudinal invariance across all three waves at the configural, metric, and partial scalar level. This allowed us to examine factor scores

for each latent variable across 9 years. Partial scalar longitudinal invariance is the minimum level of invariance required to examine differences in factor scores because the intercept for at least one of indicators has to be fixed across all three waves. In our models, for the episodic memory factor, word recall list 2 was fixed, and for the lifestyle factor, social activity variable was fixed across all three waves.

Second, higher risk scores on the demographic (see Figure 4-2), health (see Figure 4-3), and lifestyle (see Figure 4-4) factors predicted worse episodic memory performance at 75 years and steeper 9-year decline. We estimated a random intercept and random slope growth model for episodic memory and lifestyle factors. This allowed us to examine differences at the centering age of 75 years and change across a 9-year period. Several studies have used an overall risk score composite with similar variables to discriminate NA older adults from those who go on to develop dementia (Anstey et al., 2013; Anstey et al., 2014). However, we report a novel feature of calculating and examining risk scores (i.e., a lifestyle latent risk factor and risk score) to predict episodic memory performance and change in non-demented older adults. Our latent factor and growth modeling approach takes into account the shared variance in more than one lifestyle variable to create a latent construct. In addition, we use four demographic and nine health variables to create an overall demographic and health risk score. We examined three highly influential constructs rather than individual risk variables. This allowed us to examine shared risk across many variables rather than single risk variables examined in recent dementia risk score studies (Anstey et al., 2013; Barnes et al., 2009; Jessen et al., 2011; Kivipelto et al., 2006; Reitz et al., 2010).

We incorporate a broad range of risk factors and longitudinal data ranging in age from 53-95 years old. In the future, our technique can be (a) used in a variety of large population-

based settings in which a large number of risk factors need to be examined, (b) expanded by adding more risk factors as they become identified in the field, and (c) used to identify individuals who are at a high risk for decline and probable dementia in the pre-clinical phase and could benefit through enrollment in intervention programs. In the area of risk assessment tools, our novel technique provides a more robust way to assess large numbers of risk variables by grouping them into select set of risk factors (or constructs) to predict the likelihood of dementia onset (Anstey et al., 2013; Jessen et al., 2013; Kivipelto et al., 2006) and other pre-clinical cognitive markers (i.e., episodic memory trajectories). Previous studies have shown that increase in demographic, health, and lifestyle risk factors with increasing age is associated with poor cognitive performance in older adults (Fratiglioni, Paillard-Borg, & Winblad, 2004; Valenzuela, Brayne, Sachdev, & Wilcock, 2011). We extend previous studies by calculating risk scores for each risk factor and using the robust risk scores to predict cognitive outcome over time.

We now summarize several potential biological mechanisms for the three risk factors (demographic, health, lifestyle) included in our episodic memory parallel process growth model.

Demographic. The demographic risk score, comprised of the cumulative effects of age, education, gender, and marital status, predicted episodic memory performance and 9-year change. As expected, we observed that age played a major role in our demographic risk score to predict cognitive decline (Salthouse, 2009). Common age-related physical changes in the brain that lead to cognitive deficits (i.e., episodic memory impairment) include neuronal cell death resulting in gray matter shrinkage, decrease in dendritic sprouting and synaptic plasticity, white matter lesions, and increased brain volume reduction rate (Peters, 2006). Similarly, we accounted for any gender differences in our demographic risk score. Previous studies show that age-related brain changes may differ between gender, where men show greater loss in the frontal and

temporal lobes and women show increased atrophy in the hippocampus and parietal lobes (Murphy et al., 1996). In addition to age and gender, education levels also played a role in our risk composite. Previous studies have shown that low education levels may be a risk factor for dementia (Caamano-Isorna, Corral, Montes-Martinez, & Takkouche, 2006; Valenzuela et al., 2011). Higher education may contribute towards building cognitive reserve. Higher cognitive reserve may help delay pre-clinical symptoms such as memory impairment, with the same level of neuropathological brain damage (Stern, 2002; 2009) associated with a specific age group and gender. In addition, marital status is known to be an important social factor and associated with better health status compared to single older adults (Mousavi-Nasab, Kormi-Nouri, Sundström, & Nilsson, 2012). Thus, higher education levels and being married may provide a protective layer to the deleterious effects associated with age and gender. Although we are unaware of the specific contribution of each risk variable to our overall demographic risk score, we examined each risk variable to take into account any risk associated with each variable.

Health. The health risk score is comprised of the additive effects of diabetes, depression, heart disease, stroke, high blood pressure, hardening of the arteries, alcohol dependence, tobacco dependence, and traumatic brain injury. All health-related questions were based on self-report questionnaire at baseline. We note that objective measures were available for depressive affect (Center for Epidemiological Studies-Depression Scale), blood pressure (systolic and diastolic measures), and alcohol and tobacco intake (quantity per month). Future studies should consider using both objective and self-reported measures for both validating and supplementing the present approach. Approximately 33% of older adults (see Table 4-3) indicated that they had "yes, not serious" to "yes, very serious" high blood pressure. Prior reports have shown that high blood pressure in mid-life increases the chance of cognitive impairment and dementia in late

adulthood (Kivipelto et al., 2006; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). High blood pressure changes the overall vascular integrity of the blood-brain barrier through rarefaction of small vessels (Levy, Ambrosio, Pries, & Struijker-Boudier, 2001) and formation of atheromatous plaques (Kennelly, Lawlor, & Kenny, 2009), ultimately leading to brain tissue damage (Deane, Wu, & Zlokovic, 2004; Reitz & Mayeux, 2014) and hippocampal atrophy. Importantly, the hippocampus plays an important in episodic memory retrieval and storage (Glodzik et al., 2014). Older adults in our study also indicated that they had diabetes, which is a risk factor for stroke, high blood pressure, heart trouble, stroke, and hardening of the arteries (Reitz & Mayeux, 2014; Sacco et al., 1997), all included in our health risk score.

In addition, other variables in the health risk factor included depression, alcohol dependence, tobacco dependence, and head injury. Possible mechanism associated with depression and cognitive impairment may be through increased cortisol levels. High cortisol levels can lead to hippocampal atrophy, and MRI reports have shown positive correlation between depression and atrophy (Cole, Costafreda, McGuffin, & Fu, 2011). Post mortem analyses also showed that AD patients with a history of major depression have higher amyloid plaques and neurofibrillary tangles than AD patients with no history of depression (Ganguli, 2009). Although the percentage of adults in our study with alcohol dependence, tobacco dependence and some form of head injury was less than 18%, we included all three conditions to account for any changes in episodic memory performance. Previous studies report a U-shaped curve for alcohol dependence, where moderate consumption may contribute the least to cognitive impairment risk (Peters, 2012). Both smoking (Peters, 2012) and head injury (Moretti et al., 2012; Schretlen & Shapiro, 2003) have been associated with brain atrophy and poor vascular health resulting in increased dementia and cognitive impairment risk. Thus, in the present study,

the cumulative effect of a high score on vascular conditions (i.e., high blood pressure, stroke), depression, substance use, and head injury added to the risk associated with individual health conditions and predicted poor episodic memory performance and steeper decline.

Lifestyle. The latent lifestyle risk factor included the shared variance from social activities, physical activities, integrative information processing, and novel information processing. The VLS Activities Lifestyle Questionnaire has been previously validated (e.g., Hultsch et al., 1999). We note that some related objective measures were available for the domain of physical activities (i.e., timed-walk speed, hand grip strength) and future studies may consider using both objective and self-reported measures. All four lifestyle predictors have been associated with cognitive impairment in the literature. First, recent report on integrative and novel cognitive information processing showed that adults who engage in high levels of novel cognitive activities are less prone to develop cognitive impairment and dementia (Reitz & Mayeux, 2014). Second, another study found that higher level of education and social engagement in midlife or late-life was a protective factor for cognitive impairment (Valenzuela et al., 2011). Third, physical activities, such as walking have been associated with greater gray matter volume and fewer cognitive deficits (Erickson, Miller, & Roecklein, 2012).

In the present study, a high latent lifestyle risk score predicted poorer episodic memory performance and steeper decline. A possible mechanism that connects all four lifestyle risk predictors to memory decline is stress (Fratiglioni et al., 2004; Wilson et al., 2003). Stress has been associated with loss of hippocampal neurons (Bremner, 1999) resulting in learning and memory deficits. A low lifestyle risk score would mean high levels of physical and social activities, and integrative and novel information processing. Past studies have reported that adults with high levels of physical activity are more inclined to engage in novel and integrative

activities and have a greater chance of maintaining larger social networks and events (Menec, 2003). Also, a combined low lifestyle risk leads to positive state of mind and lower stress levels (Fratiglioni et al., 2004). However, our latent lifestyle risk score approach reduces the number of risk score variables examined compared to previous studies that include separate scores for each variable. Our approach provides a simpler way to account for risk associated with the lifestyle construct through the use of CFA and latent growth modeling.

Third, the synergistic effects of demographic + health risk (Figure 4- 5) and demographic + health + lifestyle risk scores (Figure 4-6) in our latent growth model showed an increased fanning effect on intercept and slope resulting in poorer episodic memory performance and steeper decline. We observed that a combined high risk score on all three risk factors showed the greatest fanning effect for episodic memory performance and decline compared to independent effect of the three risk factors. Our result provides a novel way of linking the three risk factors through synergistic effect of low, intermediate, or high risk score rather than an overall risk score (Anstey et al., 2013). Common underlying mechanisms linking all three risk factors can be a result of many different pathways. For example, regular physical activity may promote vascular health by lowering blood pressure (Warburton, Nicol, & Bredin, 2006) and generating new neurons in the hippocampus (Van Praag, Kempermann, & Gage, 1999). Increased activity and better health may lead to higher engagement in novel and integrative processing activities which can preserve or enhance cognitive abilities in old age through increased brain reserve (Wang, Karp, Winblad, & Fratiglioni, 2002). Although we examined a low, intermediate, and high-risk combination for all three risk factors in our latent growth model, we are not clear on whether the synergistic effect is simply additive or interactive. We were not able to test additive or interactive effects in our model because we explored low, intermediate, and high combination graphs based

on the results with all three risk factor scores. Therefore, to fully understand the neurobiological underpinnings of synergistic risk factor influence on episodic memory trajectories, future studies may benefit from testing specific additive and interactive associations in non-demented older adults.

We now list several strengths and limitations of the present study. For our limitations, first, all the variables included in each of the three risk domains did not receive the same amount of weight in the overall risk score. For example, some variables were added as continuous or categorical, and one risk domain was a latent factor. This limits the generalizability of our overall risk score across multiple domains with equal weightings. However, this does not affect how each risk factor predicts episodic memory in our study because all three risk factors were included in the same latent growth model. Second, although genetic risk factors are known to play a major role in episodic memory performance and change (McFall, Wiebe, Vergote, Westaway, et al., 2015), we only examined modifiable risk factors in the present study. Future studies should examine both genetic and non-genetic risk factors to provide a more comprehensive risk assessment for differential memory change in aging.

Regarding strengths, first, the VLS is a large-scale longitudinal sequential study. Thus, we had a large sample of non-demented older adults (n = 562) spanning a 40-year age band (53-95 years) from three cohorts. The large longitudinal sample size allowed us to examine intraindividual trends, stability, and variability. Second, we estimated a two-factor declarative memory and a one-factor lifestyle latent variable using six standard neuropsychological variables and four common activities of daily living, respectively. Third, we did not lose any participants as a result of missing data because all missing variables were accounted through multiple imputations.

In sum, this study built a multi-domain risk index of relatively modifiable factors to predict episodic memory performance and change in non-demented older adults. The risk index included demographic risk factor with four variables, health risk factor with nine variables, and latent lifestyle risk factor with four variables. High risk score for demographic, health, and lifestyle factors all predicted worse episodic memory at centering age 75 years and steeper 9-year decline. This risk score contributes to the growing literature on delaying cognitive decline in NA by providing a novel approach to calculate risk scores specifically for modifiable risk factors using latent growth modeling. Our study also implies that a synergistic effect of high-risk score on all three risk factors (demographic, health, lifestyle) may magnify the deleterious effect of independent risk factor on episodic memory decline.

Study 1b

Statistical Analysis

SEM was used to analyze all research goals with Mplus 7 (Muthén & Muthén, 1998-2015). All missing values were assumed to be missing at random and handled using maximum likelihood. Any missing predictor values were estimated using multiple imputations in Mplus 7. A total of 50 imputations were generated and pooled for analyses (Enders, 2011; McFall, Wiebe, Vergote, Westaway, et al., 2015; Muthén & Muthén, 1998-2015). The research goals were analyzed as follows.

Research Goal 1. We categorized all variables and created risk factors ranging from no risk (0) up to very high risk (4) for demographic (0-3), health (0-3), lifestyle (0-2), and genetic risk (0-4) factors. First, for the demographic risk composite, education (years; 0 = 14-24; 1 = 12-14; 2 = 6-12), marital status (yes = 0; no = 1), age (years; 0 < 65 years; 1 = 65-75 years; 2 = 76-85 years; 3 = 85-87 years) and gender (male = 0; female = 1) at baseline were all added to create a final score. Second, the health risk score was computed with the addition of all nine variables (diabetes, depression, heart trouble, stroke, hypertension, hardening of arteries, alcohol dependence, tobacco dependence, head injury) with higher scores representing greater risk (from no [0] to yes, very serious [3]). Third, lifestyle scores were categorized into three groups based on minimum and maximum score in the scale. The minimum score was 43 and the maximum score was 216. The risk calculation was based on this scale. The maximum score was divided by three and score at baseline was categorized as follows: 0 = 144-216; 1 = 72-144; 2 = 43-71. Higher scores represented greater risk. Fourth, formative composite genetic risk factor (Figure 4-1) and standard genetic risk score were built using different combinations of six SNPs: *COMT, BDNF, APOE, CLU*, *PICALM*, and *CR1*. For the standard genetic risk score, we created a

composite genetic risk score by simply adding the number of risk alleles for (a) 6 risk genes (*COMT, BDNF, APOE, CLU*, *PICALM*, *CR1*), (b) 4 AD risk genes (*APOE, CLU*, *PICALM*, *CR1*), and (c) *APOE* (benchmark). Similarly, the formative genetic risk score was computed using the two-factor episodic and semantic memory model for (a) 6 risk genes (*COMT*, *BDNF*, *APOE, CR1, CLU, PICALM*) and (b) 4 AD risk genes (*APOE, CR1, CLU, PICALM*) (see Figure 4-1). The formative genetic risk score model was built in Mplus using syntax for formative and CFA models. Although we only examine episodic memory in the present study, we include semantic memory because at least two factors need to be directly regressed on the composite risk score to build a formative genetic risk score (Bollen & Davis, 2009a). This rule is known as the 2+ emitted path rule (Bollen & Davis, 2009b), which states that at least two endogenous variables are required to have an identified formative composite model (Bollen & Lennox, 1991; Bollen & Bauldry, 2011; Kline, 2011, 2013; MacCallum & Browne, 1993). An under-identified model in structural equation modeling will not run a latent composite with a single direct effect. Past reports have examined latent risk in a variety of different context from business research to testing hypotheses in psychology. For example, a latent risk model included socioeconomic status, parental psychiatric behaviors, and teen verbal IQ as causal indicators, and achievement and classroom adjustment as two direct reflective factors (Worland, Weeks, Janes, & Strock, 1984). As shown in our conceptual model (Figure 4-1), 6 risk genes and 4 AD risk genes are included as causal indicators to build a formative genetic risk score. We expected to observe good model fit statistics and significant beta coefficients for the 6 gene causal indicator model and the 4 AD risk gene causal indicator model. We used continuous factor scores for the formative genetic risk to predict episodic memory performance and change. We tested model fit with several fit statistics including -2LL; χ^2; $p > .05$, RMSEA $\leq .05$, CFI $\geq .95$, and SRMR $\leq$

.08. Then we used the factor scores (as continuous) from the formative genetic risk score model to add as the genetic risk component. See Table 4-9 for details on categorization of each variable for the five risk factors.

Research Goal 2. We used the random intercept and random slope episodic memory growth model with partial scalar longitudinal invariance from Study 1a to test for differences in episodic memory performance and change. Age was centered at 75 years. All five risk factors (and all combinations) of risk factors were regressed on the episodic memory factor at baseline and at the last time point. Fifteen different combinations of risk scores were tested using the baseline risk score and final time point 3 (Wave 3) risk score as follows: (a) demographic, (b) health, (c) lifestyle, (d) demographic + health, (e) demographic + health + lifestyle, (f) standard genetic (6 genes), (g) AD standard genetic (4 AD genes) (h) *APOE* (benchmark), (i) formative genetic (6 genes), (j) AD formative genetic (4 AD genes), (k) demographic + health + lifestyle + standard genetic (6 genes), (l) demographic + health + lifestyle + AD standard genetic (4 AD genes), (m) demographic + health + lifestyle + *APOE*, (n) demographic + health + lifestyle + formative genetic risk score (6 genes), (o) demographic + health + lifestyle + AD formative genetic risk score (4 AD genes).

Research Goal 3. We examined two different methods to test risk score change on episodic memory change. First, risk score at baseline was subtracted from risk score at time point 3. The difference score was regressed on episodic memory intercept and slope for six combinations of risk factors: (a) demographic, (b) health, (c) lifestyle and (d) demographic + health + lifestyle + standard genetic (6 genes), (e) demographic + health + lifestyle + AD standard genetic (4 AD genes), (f) demographic + health + lifestyle + *APOE*. Second, growth

models were tested for risk score change to determine the best latent growth model to test parallel process model for each risk factor and episodic memory change.

Research Goal 4. We examined eleven risk factor combinations to test whether the risk factors discriminated NA older adults from MCI adults. We used receiver operating characteristic (ROC) curve analyses using SPPS 22 for Windows (SPSS Inc., Chicago, IL, USA) for the following risk factors: (a) demographic, (b) health, (c) lifestyle, (d) demographic + health, (e) demographic + health + lifestyle, (f) standard genetic (6 genes), (g) AD standard genetic (4 AD genes) (h) *APOE*, (i) demographic + health + lifestyle + standard genetic (6 genes), (j) demographic + health + lifestyle + AD standard genetic (4 AD genes), and (k) demographic + health + lifestyle + *APOE*. The area under the curve (AUC) for all ROC analyses determined which risk score significantly discriminated clinical status (NA versus MCI).

Results

Research Goal 1. Based on the existing literature, we categorized all variables and created risk scores ranging from no risk (0) up to very high risk (4) for the combination of demographic, health, and lifestyle risk factors. See Table 4-9 for complete detail on categorization of each variable in the five risk factors. For the genetic risk factor, we created a standard composite genetic risk score and a formative genetic risk score using 6 genes, 4 AD genes, and *APOE*. For the formative model, we used (a) 6 genes and (b) 4 AD genes as formative indicators and two-factor episodic and semantic memory latent constructs as reflective indicators. This model did not converge. Second, we tested a formative genetic risk model with (a) 6 genes and (b) 4 AD genes as causal indicators and episodic memory latent factor from time point 1 to 3 as reflective indicators. This model also did not result in convergence. Third, we tested a formative genetic risk model with (a) 6 genes and (b) 4 AD genes as causal indicators

and four episodic memory measures (Word Recall 1, Word Recall 2, REY list A6, REY list B1) as separate reflective indicators. This model resulted in good model fit statistics for (a) 6 genes (AIC = 9407.04; BIC = 9484.09; $\chi^2(df)$ = 47.21 (20), p = .001; *RMSEA* (90% CI) = .050 (.032-.069); *CFI* = .926; and *SRMR* = .035) (see Table 4-10; Figure 4-7) and (b) 4 AD genes (AIC = 9405.37; BIC = 9473.86; $\chi^2(df)$ = 43.80 (14), p < .001; *RMSEA* (90% CI) = .063 (.043-.085); *CFI* = .919; and *SRMR* = .041) (see Table 4-10). Factor scores were computed for (a) 6 genes and (b) 4 AD genes to use as the final formative genetic risk score for each adult.

Research Goal 2. Twelve of fifteen different combinations of baseline or time point 3 risk scores significantly predicted episodic memory intercept and/or slope. The following three independent risk scores were significant predictors: (a) demographic (baseline slope: β = -0.005; SE = 0.002; p = 0.004; time point 3 slope: β = -0.005; SE = 0.002; p = 0.001), (b) health (baseline intercept: β = -0.069; SE = 0.034; p = 0.042; baseline slope: β = -0.004; SE = 0.001; p = 0.000; time point 3 intercept: β = -0.071; SE = 0.026; p = 0.006; time point 3 slope: β = -0.003; SE = 0.001; p = 0.006), and (c) lifestyle (baseline intercept: β = -0.252; SE = 0.111; p = 0.023; time point 3 slope: β = -0.014; SE = 0.005; p = 0.006).

The following combined risk scores were significant predictors: (d) demographic + health (baseline intercept: β = -0.055; SE = 0.027; p = 0.041; baseline slope: β = -0.003; SE = 0.001; p = 0.000; time point 3 intercept: β = -0.059; SE = 0.021; p = 0.005; time point 3 slope: β = -0.003; SE = 0.001; p = 0.000) and (e) demographic + health + lifestyle (baseline intercept: β = -0.059; SE = 0.026; p = 0.024; baseline slope: β = -0.003; SE = 0.001; p = 0.000; time point 3 intercept: β = -0.060; SE = 0.020; p = 0.003; time point 3 slope: β = -0.003; SE = 0.001; p = 0.000).

The following genetic-related predictors were significant: (f) formative genetic (6 genes) (intercept: β = 1.139; SE = 0.039; p = 0.000; slope: β = 0.022; SE = 0.003; p = 0.000), (g) AD

formative genetic (4 AD genes) (slope: β = 0.005; SE = 0.002; *p* = 0.021); (h) demographic + health + lifestyle + standard genetic (6 genes) (baseline slope: β = -0.002 ; SE = 0.001; *p* = 0.003; time point 3 intercept: β = -0.044; SE = 0.018; *p* = 0.015; time point 3 slope: β = -0.002; SE = 0.001; *p* = 0.001), (i) demographic + health + lifestyle + AD standard genetic (4 AD genes) (baseline slope: β = -0.002; SE = 0.001; *p* = 0.006; time point 3 intercept: β = -0.043; SE = 0.020; *p* = 0.028; time point 3 slope: β = -0.002; SE = 0.001; *p* = 0.001), (j) demographic + health + lifestyle + *APOE* (baseline slope: β = -0.003; SE = 0.001; *p* = 0.001; time point 3 intercept: β = -0.053; SE = 0.021; *p* = 0.011; time point 3 slope: β = -0.003; SE = 0.001; *p* = 0.001), (k) demographic + health + lifestyle + formative genetic (6 genes) (baseline intercept: β = 0.090; SE = 0.023; *p* = 0.000; time point 3 intercept: β = 0.055; SE = 0.023; *p* = 0.016), (l) demographic + health + lifestyle + AD formative genetic (4 AD genes) (baseline slope: β = -0.002; SE = 0.001; *p* = 0.003; time point 3 slope: β = -0.002; SE = 0.001; *p* = 0.008) (see Table 4-11). With one exception, higher risk scores were associated with poorer episodic memory performance and steeper decline. The exception was the formative genetic risk score with six genes. Unexpectedly, higher formative genetic risk scores were associated with better episodic memory performance at age 75 years and an increase in performance with age. However, higher AD formative genetic risk score with 4 AD-related genes was associated with steeper episodic memory decline. We did not observe significant differences on episodic memory intercept or slope with the standard genetic risk predictor with 6 genes, 4 AD genes, or *APOE*.

***Research Goal 3*.** Two different methods were applied to test risk score change on episodic memory change. First, risk score at baseline was subtracted from risk score at time point 3. The risk score difference did not significantly predict episodic memory performance at age 75 or change for any of the six combinations of risk scores (see Table 4-12). Second, the random

intercept and fixed slope was the best growth model for all nine risk score combinations. With no change in slope, we did not examine parallel process growth models for risk score and episodic memory associations.

Research Goal 4. Demographic and health risk scores significantly discriminated the NA group from the MCI group. As expected, the MCI group had higher demographic risk scores as compared to NA older adults (AUC = 0.622; $p = 0.001$). However, higher health risk scores were observed in the NA group than in the MCI group (AUC = 0.368; $p = 0.003$). No other risk score combinations significantly discriminated NA group from the MCI group (see Table 4-13).

Discussion

In Study 1b, our main goals were (a) to build a multi-domain risk index using demographic, health, lifestyle and select genetic polymorphisms to (b) predict episodic memory performance and change and (c) distinguish NA older adults from those with MCI. We used the previously confirmed partial scalar, and random intercept and random slope episodic memory latent growth model from Study 1a. We applied a recently used technique to categorize and build demographic, health, lifestyle, and standard genetic risk scores (Anstey et al., 2014; Barnes et al., 2009; Jessen et al., 2011; Kivipelto et al., 2006). In addition, we used several different novel techniques to advance the growing field of dementia and cognitive aging risk score calculation to predict cognitive impairment and dementia. First, we generated a standard genetic risk score by adding the number of risk alleles for 6 genes (*APOE, COMT, BDNF, CLU, CRI*, and *PICALM*) commonly associated with cognitive decline and dementia, 4 AD genes (*APOE, CLU, CRI*, and *PICALM*), and *APOE* (Bartres-Faz et al., 2002; Dixon et al., 2014; Ghisletta et al., 2014; Harold et al., 2009; McFall et al., 2013; Papenberg et al., 2014; Wishart et al., 2011). Second, we explored the effects of a novel formative genetic risk score with all 6 genes (*APOE, COMT,*

BDNF, CLU, CRI, and *PICALM*) and 4 AD genes (*APOE, CLU, CRI*, and *PICALM*) as formative indicators and episodic memory indicators (Word Recall 1, Word Recall 2, REY list A6, REY list B1) as reflective indicators (see Figure 4-7). Third, we tested both independent and cumulative (additive) effects of all five risk scores to predict episodic memory performance at baseline and time point 3. Fourth, we calculated change in risk score to predict change in episodic memory performance over 9 years. Fifth, we applied different combinations of additive risk scores to test which combination is the most sensitive to distinguish NA versus MCI status.

This is the first study to examine three modifiable risk factors (demographic, health, lifestyle) and six genetic risk polymorphisms (*APOE, COMT, BDNF, CLU, CR1, PICALM*) to test episodic memory performance at age 75 years and 9-year change in non-demented older adults. In addition, we tested three variables to distinguish two clinical groups (NA versus MCI). Three key findings of the present study are as follows. First, we predicted episodic memory performance and change at two time points using both independent and cumulative (additive) risk score for demographic, health, lifestyle, and genetic risk factors. Second, we calculated 9-year difference in risk score, but this did not predict episodic memory change in our sample. Third, we observed that demographic and health risk scores significantly distinguished NA group from the MCI group. We now discuss research goals 1-4.

Research Goal 1. We created risk scores for all five risk factors (demographic, health, lifestyle, standard genetic, formative genetic) and the novel formative genetic risk score with four episodic memory indicators provided good model fit statistics. Specifically for standard and formative genetic risk scores, we examined six genetic polymorphisms in three different combinations: (a) an overall additive effect of six genes (*APOE, CLU, CR1, PICALM, COMT, BDNF*), (b) AD risk genes (*APOE, CLU, CR1, PICALM*) to examine an overall AD genetic risk

score (McFall et al., 2015), and (c) independent effect of *APOE* based on the literature with *APOE* and dementia risk score (Kivipelto et al., 2006).

Research Goal 2. We examined independent and additive models for all risk factors to predict episodic memory performance and 9-year change at baseline and time point 3. Higher risk scores at baseline and time point 3 were associated with poorer episodic memory performance at 75 years and steeper 9-year decline for (a) independent risk factors (demographic, health, lifestyle), (b) cumulative risk factors (demographic + health, demographic + health + lifestyle), and (c) cumulative genetic and non-genetic risk factors (demographic + health + lifestyle + standard genetic, demographic + health + lifestyle + AD standard genetic, demographic + health + lifestyle + *APOE*) (see Table 4-11). This suggests that the mechanism through which genetic risk factors and modifiable risk factors influence cognitive decline may be dependent on the aggregate of each risk factor than risk associated with single variables. Previous studies have only examined the *APOE* gene with modifiable risk factors (Barnes et al., 2009; Kivipelto et al., 2006; Reitz et al., 2010). We examined cumulative risk scores with five additional genetic polymorphisms and three modifiable risk factor scores over 9 years. The present cumulative risk score provides a novel approach to combine a multitude of both modifiable (demographic, health, and lifestyle) and non-modifiable (genes) risk variables to test the overall risk associated with each risk domain independently and synergistically.

As expected, we observed that higher AD formative genetic risk score was associated with steeper 9-year episodic memory decline. Although, we did not observe all favorable independent results, both standard and formative genetic risk scores contributed to the overall risk associated with modifiable risk scores. This result suggests that examining specific combinations of genes (i.e., only AD risk genes) may advance cognitive aging risk prediction

through the use of formative genetic risk models. Future studies should consider examining different combination of genes to calculate genetic risk scores rather than single candidate gene association studies to predict cognitive performance, which may provide additional insight on the specific combinations of genes associated with cognitive decline.

As predicted, our risk score differentiated between adults who had poor episodic memory performance and steep decline based on their risk factor profiles. We observed that there were no significant differences for episodic memory performance at age 75 years and 9-year change whether the baseline or time point 3 risk scores were used. This implies that (a) there were no significant changes in risk score over 9 years or (b) adults in our sample did not change much in their health and lifestyle risk factors between baseline and time point 3. Although we did not have a younger sample, our finding supports previous results which show that changes or habits at an earlier age are a strong predictor of later-life cognitive performance. For example, studies have observed that midlife blood pressure predicts cognitive decline and brain atrophy in later life (Swan et al., 1998), midlife cardiovascular risk factors increase the chance of late-life dementia onset (Whitmer et al., 2005), midlife vascular risk factors play a role in MCI development (Kivipelto et al., 2001), and midlife hypertension, diabetes, smoking, and obesity levels may predict vascular brain injury, hippocampal atrophy and executive function (EF) decline 10 years later (Debette et al., 2011). Overall changes in health and lifestyle factors did not contribute to the overall risk score. Future large randomized controlled trials may benefit from closely monitoring modifiable risk factors starting from a young age to identify adults with significant health and lifestyle changes.

Research Goal 3. We used two different techniques to calculate change in risk score and predict episodic memory change by (a) estimating a latent growth model for risk scores and (b)

calculating a change score between time point 1 and 3. We used the latent growth model because it allows us to examine interindividual differences in change over time and test both time varying and time-invariant predictors in one model (Kline, 2013). We used change or difference scores because it is a simple and quick method that can be used in most situations with single predictor variables. However, raw score differences cannot be compared across predictors with different scales. For the latent growth model, we estimated a random intercept and fixed slope growth model for all nine risk score combinations. This means that older adults in our sample all had the same rate of risk score change over time. For the calculated change risk scores, we observed no significant changes in episodic memory over 9 years. This result implies that (a) NA adults in our sample did not have significant changes in their risk score profiles in the three risk domains (demographic, health, lifestyle) between baseline and time point 3 and (b) adults with high risk scores at baseline also had a high risk score at time point 3, which predicted episodic memory decline. We only examined non-demented older adults in our analyses and significant changes in risk factor profiles (i.e., deteriorating vascular health and decreased physical activity) may occur in adults who go on to develop severe memory impairment. Previous studies have only examined risk factors to predict cognitive changes (Anstey & Christensen, 2000) or that cognitive changes may account for the differences observed in late life activities (Hultsch, Hertzog, Small, & Dixon, 1999). Thus, future studies should consider examining changes in risk scores to identify those who go from low to a high risk score and also show increased rate of cognitive decline.

Research Goal 4. Demographic and health risk scores distinguished the NA and MCI groups. As expected, we observed that the MCI group had higher demographic risk scores. This suggests and supports past findings that adults in the MCI group are more likely to be female, not married, older, and have lower education levels (Dolcos et al., 2012; Tervo et al., 2004).

However, for the health risk score, we observed that higher health risk score was present in the NA group. Based on previous reports (Tervo et al., 2004; Zou et al., 2014), we expected poorer overall health in the MCI group. Although the specific neural underpinnings for each variable are still unclear, we explore some potential mechanisms associated with the demographic and health risk factors. For demographic, higher education levels and marital status in old age may provide greater social engagement, and a cognitively stimulating and active lifestyle resulting in higher cognitive reserve (Stern, 2009). High cognitive reserve is associated with greater and efficient recruitment of brain networks and compensation strategies to account for memory decline associated with aging. For health, vascular risk factors such as lower blood pressure in old age may accelerate episodic memory decline through decreased cerebral blood flow (Henry-Fugeas, 2008). A recent meta-analysis showed that diabetes incidence is associated with increased risk for MCI (Cheng, Huang, Deng, & Wang, 2012). Specifically, white matter hyperintensities, brain infarcts, hyperinsulinemia, and advanced products of glycosilation are commonly associated underlying processes and conditions linking diabetes to cognitive impairment and AD (Luchsinger, 2012).

We now list several strengths and limitations of the present study. For our limitations, first, we used list-wise deletion for any missing predictor variables. This reduced our overall sample size in both the NA group and the MCI group, but we still had an overall large sample size $n = 562$ in the NA group and $n = 69$ in the MCI group at baseline. Second, although we included a large sample size for our NA group, our MCI sample size was considerably smaller compared to the NA group. A similar sample size would have reduced the confidence interval differences (Lasko, Bhagwat, Zou, & Ohno-Machado, 2005) and resulted in a more precise ROC estimate. Third, the contribution of the episodic memory variables in the formative genetic risk

score is not clear, but we know that the overall risk score accounted for each person's genetic risk which was then used to take into account the episodic memory indicators (Bollen, 2011). As we observed that higher formative genetic risk score with 6 genes and lower AD formative genetic risk score with 4 AD risk genes was associated with better episodic memory performance at age 75 years and increase in performance with age, we decided not to test this overall risk to differentiate between NA and MCI status. It is important to note that we tested a novel method of examining genetic risk factors that should be examined in future genetic and cognitive association studies to explore potential underlying mechanisms through which genetics and cognitive performance influences dementia onset and development.

For our strengths, first, we included a large sample of NA older adults (n = 562) spanning a 40-year age band (53-95 years), a large number of variables for demographic, health, and lifestyle risk domains and six genetic polymorphisms. Previous studies (e.g., Anstey et al., 2014; Kivipelto et al., 2006) have not examined such a large dataset with a broad range of risk predictors in one study. Second, all the variables included in each of the four risk factors (except for the formative genetic risk factor) received equal weights in the overall risk score ranging from 0 to 3. This allowed us to compare risk scores between domains, including standard genetic risk. Third, we used a latent growth model for our dependent variable, episodic memory performance and change, which accounted for measurement errors associated with single predictor variables commonly represented in the literature.

In sum, we focused on the traditionally represented categorical method for dementia risk indices in the literature to expand and explore different techniques (i.e., latent growth modeling, change scores, formative composite genetic risk score) to predict episodic memory performance and distinguish between NA versus MCI clinical status. Regarding risk factors, we included a

large and broad range of risk factors than previously reported in the literature. Our overall risk index included genetic, demographic, health, and lifestyle risk factors. The different techniques applied in our risk score calculation and prediction allows us to conclude that: (a) change in risk score does not always predict change in cognitive performance, (b) addition of formative genetic and standard genetic risk scores may contribute to the overall modifiable risk score, and (c) differentiating between clinical statuses may be more successful with independent risk factors and not always through additive effects of risk factors. Specifically, the underlying mechanisms may differ between those who go on to develop MCI and those who show normal trajectories of cognitive decline.

Conclusion

Recent single factor epidemiological studies report inconsistent findings with modifiable and non-modifiable risk factors associated with cognitive impairment. It has become imperative to take a multimodal approach to examine complex cognitive aging trajectories to delay cognitive decline and dementia incidence (Olanrewaju et al., 2015). We examined a large dataset with comprehensive set of demographic, health, lifestyle, and genetic variables to build a multidimensional risk index to predict episodic memory performance and decline, and discriminate NA group from MCI. Study 1a examined modifiable risk factors to focus on risk factors that may be used in future dementia prevention trials and intervention program. This is the first study to use latent constructs and ~9 years of longitudinal data (three time points) with risk scores to test change in episodic memory, a pre-clinical marker for dementia. Risk scores were based on a broad range of risk factors which may help target individual-specific dementia prevention strategies. Study 1b examined both modifiable and non-modifiable (genetic) risk factors to examine overall risk on episodic memory trajectories and discriminate two clinical groups (NA versus MCI). Study 1b examined six genetic polymorphisms to identify genetic factors that may have small effects independently but in synergy make a significant difference on cognitive aging trajectories. In addition, we used advanced statistical modeling to introduce the concept of novel formative latent risk scores. Taken together, both Studies 1a and 1b contribute to the growing literature on cognitive aging and advance the dementia risk score field through (a) novel and advanced statistical methods for calculating risk scores, (b) inclusion of both genetic and modifiable risk factors in one risk score, and (c) broad range of risk variables examined across a 9-year period. Future studies can take our approach to identify those at high risk for cognitive decline or dementia (i.e., examining decline in episodic memory trajectories) and target

intervention programs through a multi-domain and individually tailored approach to older adults. Future studies should also consider examining other risk factors not included in this study (i.e., nutrition information, pesticide exposure) and different statistical approaches (i.e., interactive) that may provide further insight into the potential mechanisms associated with risk scores.

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Table 4-1

Mean (standard deviation) demographics and genotype by time point for normal aging group and mild cognitive impairment group

Normal Aging	**T1**	**T2**	**T3**
n	562	505	477
Gender (% female)	68.00	--	--
Age (years)	68.32 (7.68)	73.02 (7.69)	77.08 (7.39)
Range (years)	53-87	57-91	62-95
Education (years)	15.40 (2.94)	15.51 (2.88)	15.42 (3.06)
Mini-Mental State Exam	28.86 (1.12)	28.66 (1.17)	28.37 (2.03)
Marital Status (% married)	63.00	51.10	42.30
COMT (A/A; A/G; G/G)	132/304/132	--	--
BDNF (G/G; G/A; A/A)	375/169/24	--	--
APOE (ε2/ε2; ε2/ε3; ε3/ε3; ε3/ε4; ε4/ε4)	36/36/340/117/11	--	--
CLU (T/T; T/C; C/C)	95/286/187	--	--
CR1(G/G; G/A; A/A)	194/297/77	--	--
PICALM (C/C; C/T; T/T)	134/216/217	--	--
Mild Cognitive Impairment			
n	69	69	--
Gender (% female)	56.5	--	--
Age (years)	73.36 (5.47)	78.09 (5.37)	--
Range (years)	64-91	68-95	--
Education (years)	14.26 (3.01)	--	--
Mini-Mental State Exam	28.38 (1.30)	--	--
Marital Status (% married)	72.1	--	--
COMT (A/A; A/G; G/G)	15/35/19	--	--
BDNF (G/G; G/A; A/A)	46/20/3	--	--
APOE (ε2/ε2; ε2/ε3; ε3/ε3; ε3/ε4; ε4/ε4)	2/6/38/20/1	--	--
CLU (T/T; T/C; C/C)	10/31/27	--	--

CR1(G/G; G/A; A/A)	23/36/9	--	--
PICALM (C/C; C/T; T/T)	17/21/30	--	--

Note. T = Time point. *COMT = Catechol-O-methyltransferase; BDNF = Brain-derived neurotrophic factor; APOE = Apolipoprotein E; CLU = Clusterin; CR1 = Complement receptor 1*; *PICALM = Phosphatidylinositol-binding clathrin assembly protein.*

Table 4-2

Literature sources for risk factors

Risk Factors	**Indicators**	**Literature**	**Direction in Present Study**
Demographic	Education	Springer et al., 2005	Higher = Less risk
	Marital Status	Seeman et al., 2001	Married = Less risk
	Age	Bäckman et al., 2000	Older = More risk
	Gender	Bartrés-Faz et al., 2002	Female = More risk
Active lifestyle	Social Activities	Small et al., 2012	Higher activities = Less risk
	Physical Activities	Bherer et al., 2013; Small et al., 2012	Higher activities = Less risk
	Integrative Information	Hultsch et al., 1999; Small et al., 2012	Higher activities = Less risk
	Novel Information	Hultsch et al., 1999; Small et al., 2012	Higher activities = Less risk
Health	Diabetes	McFall et al., 2013	Diabetic = More risk
	Depression	Lichtenberg et al., 1995	Depression = More risk
	Heart Disease	Dardiotis et al., 2012	Heart disease = More risk
	Stroke	Kalaria & Balldard, 2001	Stroke = More risk
	High Blood Pressure	Kilander et al., 1997	High Blood Pressure = More risk
	Hardening of the Arteries	Hanon et al., 2005	Hardening of the Arteries = More risk
	Alcohol Dependence	Hoang et al., 2014	Dependent = More risk
	Tobacco Dependence	Sabia et al., 2012	Dependent = More risk
Genetic	*COMT*	Wishart et al., 2011	Risk allele: G+
	BDNF	Nagel et al, 2008	Risk allele: A+
	APOE	Brainerd et al., 2011	Risk allele: ε4+
	CLU	Thambisetty et al., 2013	Risk allele: C+
	CR1	Chibnik et al., 2011	Risk allele: A+
	PICALM	Ferencz et al., 2014	Risk allele: T+

Note. COMT = Catechol-O-methyltransferase; BDNF = Brain-derived neurotrophic factor; APOE = Apolipoprotein E; CLU = Clusterin; CR1 = Complement receptor 1; *PICALM = Phosphatidylinositol-binding clathrin assembly protein.*

Table 4-3

Mean (standard deviation) for risk factors by time point for normal aging older adults

	T1	T2	T3
Demographic			
Age (years)	68.32 (7.68)	73.02 (7.69)	77.08 (7.39)
Gender (% female)	68.00		
Education (years)	15.40 (2.94)	15.51 (2.88)	15.42 (3.06)
Marital Status (% married)	63.00	51.10	42.30
Health			
Diabetes (a/b/c/d)	527/20/12/0	462/25/16/0	395/27/15/1
Stroke (a/b/c/d)	543/14/3/0	487/9/6/0	418/11/8/1
Depression (a/b/c/d)	443/69/39/9	394/75/29/5	351/60/23/3
Head Injury (a/b/c/d)	471/42/13/0	432/49/22/0	378/44/15/1
Heart Trouble (a/b/c/d)	459/61/23/16	384/57/40/22	324/47/49/18
High Blood Pressure (a/b/c/d)	374/122/61/3	270/152/79/2	219/146/69/4
Hardening of Arteries (a/b/c/d)	525/18/12/2	460/23/14/5	391/28/16/3
Alcohol Dependence (a/b/c/d)	541/12/3/3	483/11/7/2	420/12/2/3
Tobacco Dependence (a/b/c/d)	553/5/2/0	494/4/5/0	431/6/0/0
Active Lifestyle			
Physical Activities	15.93 (4.98)	15.23 (5.05)	14.16 (5.19)
Social Activities	22.68 (6.64)	22.39 (6.67)	21.22 (6.92)
Integrative Information Processing	19.92 (9.14)	18.47 (9.05)	17.28 (8.82)
Novel Information Processing	77.76 (16.42)	76.12 (16.03)	73.85 (16.01)

Note. T = Time point; a = No; b = Yes, not serious; c = Yes, moderately serious; d = Yes, very serious.

Table 4-4

Mean (standard deviation) for episodic and semantic memory measures by time point

	T1	**T2**	**T3**
Episodic Memory			
Word Recall List 1	17.71 (4.58)	17.71 (4.58)	16.32 (4.73)
Word Recall List 2	19.23 (4.64)	18.77 (4.66)	17.67 (4.98)
REY List A6	10.65 (7.01)	9.36 (3.24)	8.68 (3.20)
REY List B1	6.70 (6.84)	5.60 (1.75)	5.04 (1.65)
Semantic Memory			
Vocabulary	43.69 (5.99)	44.17 (5.27)	38.52 (15.12)
Fact Recall 1	21.71 (6.37)	21.56 (6.58)	19.93 (6.90)
Fact Recall 2	21.22 (6.25)	21.18 (6.43)	19.87 (6.74)

Note. T = Time point; REY = Rey Auditory Verbal Learning Test.

Table 4-5

Study 1a (Research goal 1): Confirmatory factor analysis model fit statistics for lifestyle risk, and two-factor episodic and semantic memory constructs from time point 1 to 3

Model	AIC	BIC	$\chi^2_M(df_M)$	RMSEA (90% CI)	CFI	SRMR
Lifestyle						
T1	15492.419	15566.355	4.790 (2); $p = 0.091$	0.050 (0.000-0.109)	0.985	0.019
T2	13923.429	13974.004	3.895 (2); $p = 0.143$	0.044 (0.000-0.108)	0.992	0.016
T3	11641.704	11690.101	3.192 (2); $p = 0.203$	0.038 (0.000-0.111)	0.995	0.017
Two-factor EM and SM						
T1	19950.737	20054.693	43.847 (11); $p = 0.000$	0.073 (0.051-0.096)	0.974	0.038
T2	18884.312	18985.749	22.342 (11); $p = 0.022$	0.045 (0.017-0.072)	0.992	0.029
T3	17557.839	17658.554	29.837 (11); $p = 0.002$	0.059 (0.034-0.085)	0.986	0.059

Note. AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; χ^2_M = Chi-square test of model fit; df_M = Degrees of freedom for model fit; RMSEA = Root Mean Square Error of Approximation; CI = Confidence Interval; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; T = Time point; EM = Episodic Memory; SM = Semantic Memory.

Table 4-6

Study 1a (Research goal 2): Longitudinal measurement invariance model fit statistics and chi-square difference test for lifestyle and episodic and semantic memory constructs from time point 1 to 3

Model	AIC	BIC	$\chi^2_M(df_M)$	RMSEA (90% CI)	CFI	SRMR	χ^2_D (df_D)
Active lifestyle							
Configural	38121.770	38242.219	52.736 (39); p = 0.070	0.025 (0.000-0.041)	0.996	0.025	--
Metric	38122.356	38137.752	65.321 (45); p = 0.025	0.028 (0.000-0.042)	0.994	0.034	12.585 (6)*
Scalar	38287.315	38447.974	246.280 (53); p = 0.000	0.080 (0.070-0.090)	0.947	0.0062	180.959 (8)**
Partial scalar[a]	38156.490	38343.201	103.455 (47); p = 0.000	0.046 (0.034-0.058)	0.984	0.040	38.134 (2)**
EM							
Configural	27275.517	27496.966	70.567 (39); p = 0.002	0.038 (0.023-0.052)	0.988	0.036	--
Metric	27269.506	27464.902	76.555 (45); p = 0.002	0.035 (0.021-0.048)	0.988	0.045	5.998 (6)
Scalar	27559.996	27720.654	383.045 (53); p = 0.000	0.105 (0.095-0.115)	0.875	0.104	306.49 (8)**
Partial scalar[b]	27344.710	27531.421	155.759 (47); p = 0.000	0.064 (0.053-0.075)	0.959	0.058	79.204 (2)**
SM							
Configural	26576.305	26745.648	38.370 (15); p = 0.001	0.052 (0.032-0.073)	0.994	0.014	--
Metric	26576.930	26728.904	46.994 (19); p = 0.000	0.051 (0.033-0.069)	0.993	0.040	8.624 (4)
Scalar	26744.864	2680.785	226.928 (25); p = 0.000	0.119 (0.105-0.134)	0.949	0.080	179.934 (6)**
Partial scalar[b]	26642.845	26786.135	116.909 (21); p = 0.000	0.090 (0.074-0.106)	0.976	0.057	69.915 (2)**

Note. AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; χ^2_M = Chi-square test of model fit; df_M = Degrees of freedom for model fit; RMSEA = Root Mean Square Error of Approximation; CI = Confidence Interval; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; X^2_D = Chi-square test of difference; df_D = Degrees of freedom for difference in model fit; EM = Episodic Memory; SM = Semantic Memory.

[a]Partial scalar, where the intercept for social activity is constrained to be equal across all three time points.

[b]Partial scalar, where the intercept for word recall list 2 is constrained to be equal across all three time points.

[c]Partial scalar, where the intercept for vocabulary is constrained to be equal across all three time points.

*p<.05; **p<.001.

Table 4-7

Study 1a (Research goal 3): Latent growth model fit statistics and chi-square difference test for lifestyle and episodic memory constructs by age

Model	H0 value	Free Parameters	-2LL	AIC	BIC	D (df_D)
Lifestyle						
Fixed Intercept	-2171.699	4	4343.398	4351.399	4368.767	--
Random Intercept	-818.402	5	1636.804	1646.804	1668.514	2706.594 (1)
Random Intercept, Fixed Slope	-808.475	6	1616.95	1628.475	1628.949	19.854 (1)**
Random Intercept, Random Slope	-786.685	8	1573.370	1589.369	1624.106	43.58 (2)**
Random Intercept, Random Slope, Fixed Quadratic	-1246.261	9	2492.522	2510.522	2549.601	-919.152 (1)
EM						
Fixed Intercept	-2494.624	4	4989.248	4997.248	5014.617	--
Random Intercept	-930.576	5	1861.152	1871.152	1892.862	3128.096 (1)
Random Intercept, Fixed Slope	-891.486	6	1782.972	1794.973	1821.025	78.18 (1)**
Random Intercept, Random Slope	-559.743	8	1119.486	1135.485	1170.222	663.486 (2)**
Random Intercept, Random Slope, Fixed Quadratic	-1235.473	9	2470.946	2488.945	2528.024	-1351.46 (1)

Note. H0 = Log Likelihood; -2LL = -2 Log Likelihood; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; D = Deviance statistic; df_D = Degrees of freedom for difference in deviance statistics; EM = Episodic Memory.
*p<.05; **p<.001.

Table 4-8

Study 1a (Research goal 3): Parallel process model fit statistics for lifestyle, demographic, and health risk factors regressed on episodic memory intercept and slope

Model	**Model Results**			**Model Fit Statistics**				
	Est.	**S.E.**	***p***	**H0 value**	**Free Parameters**	**-2LL**	**AIC**	**BIC**
EM Intercept: -0.338				-1303.904	23	2607.808	2653.807	2753.676
Lifestyle intercept	-0.272	0.055	0.000					
Health	-0.061	0.027	0.024					
Demographic	-0.034	0.016	0.034					
EM Slope: -0.018								
Lifestyle intercept	-0.003	0.002	0.248					
Lifestyle slope	-0.448	0.150	0.003					
Health	-0.002	0.001	0.003					
Demographic	-0.001	0.001	0.034					

Note. Est. = Regression Estimate; SE = Standard Error; EM = Episodic Memory; H0 = Log Likelihood; -2LL = -2 Log Likelihood; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria.

Table 4-9

Study 1b (Research goal 1): Categorizing demographic, lifestyle, health, and genetic risk factors from no risk to very high risk

Demographic risk			
Education	Gender	Marital Status	Age
0 >14	0 = Male	0 = married	0 < 65 years
1 = 12-14	1 = Female	1 = not married	1 = 65-75 years
2 < 12			2 = 76-85 years
			3 > 85 years
Lifestyle factor risk			
0 > 144	Novel information, integrative information, social activities, and physical activities were added for a composite score at each wave (minimum = 43 and maximum = 216). This was then divided by 3 to create low, moderate, and high risk groups for the risk score.		
1 = 72-144			
2 < 72			
Health risk			
0 = No	Diabetes	Depression	Heart trouble
1 = Yes, not serious	Stroke	Hypertension	Hardening of arteries
2 = Yes, moderately serious	Alcohol dependence	Head Injury	Tobacco dependence
3 = Yes, very serious			
Standard genetic risk			
0 = Homozygote no risk	*COMT*	*BDNF*	*APOE* (ε2/ε4 group was deleted). Coded from 0-4 – was given more weight based on the literature.
1 = Heterozygote	*PICALM*	*CR1*	
2 = Homozygote risk	*CLU*		
Formative genetic risk			
Continuous			

Note. COMT = Catechol-O-methyltransferase; BDNF = Brain-derived neurotrophic factor; APOE = Apolipoprotein E; CLU = Clusterin; CR1 = Complement receptor 1; *PICALM = Phosphatidylinositol-binding clathrin assembly protein.*

Table 4-10

Study 1b (Research goal 1): Building the formative genetic risk composite - confirmatory factor analysis model fit statistics

Model	AIC	BIC	$\chi^2_M(df_M)$	RMSEA (90% CI)	CFI	SRMR
Genetic risk (EM and SM)[a]			No convergence			
Genetic risk (EM T1-T3)[b]			No convergence			
Genetic risk (EM indicators)[c]	9407.038	9484.085	47.209 (20); $p = 0.001$	0.050 (0.032-0.069)	0.926	0.035
AD genetic risk (EM and SM)[d]			No convergence			
AD genetic risk (EM T1-T3)[e]			No convergence			
AD genetic risk (EM indicators)[f]	9405.371	9473.857	43.800 (14); $p < 0.001$	0.063 (0.043-0.085)	0.919	0.041

Note. AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; χ^2_M = Chi-square test of model fit; df_M = Degrees of freedom for model fit; RMSEA = Root Mean Square Error of Approximation; CI = Confidence Interval; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; T = Time point; *COMT = Catechol-O-methyltransferase; BDNF = Brain-derived neurotrophic factor; APOE = Apolipoprotein E; CLU = Clusterin; CR1 = Complement receptor 1*; *PICALM = Phosphatidylinositol-binding clathrin assembly protein.*

[a]Formative genetic risk composite includes *APOE, COMT, BDNF, CLU, CRI*, and *PICALM* as formative indicators and two-factor episodic and semantic memory latent constructs as reflective indicators.

[b]Formative genetic risk composite includes *APOE, COMT, BDNF, CLU, CRI*, and *PICALM* as formative indicators and episodic memory latent factor from time point 1 to 3 as reflective indicators.

[c]Formative genetic risk composite includes *APOE, COMT, BDNF, CLU, CRI*, and *PICALM* as formative indicators and episodic memory indicators (Word Recall List 1, Word Recall List 2, REY List A6, REY List B1) as reflective indicators.

[d]Formative genetic risk composite includes *APOE, CLU, CRI*, and *PICALM* as formative indicators and two-factor episodic and semantic memory latent constructs as reflective indicators.

[e]Formative genetic risk composite includes *APOE, CLU, CRI*, and *PICALM* as formative indicators and episodic memory latent factor from time point 1 to 3 as reflective indicators.

[f]Formative genetic risk composite includes *APOE, CLU, CRI*, and *PICALM* as formative indicators and episodic memory indicators (Word Recall List 1, Word Recall List 2, REY List A6, REY List B1) as reflective indicators.

Table 4-11

Study 1b (Research goal 2): Baseline and time point 3 risk scores regressed on episodic memory intercept and slope

Risk Score	**Model Results**			**Model Fit Statistic**				
	Est.	**S.E.**	***p***	**H0 value**	**Free Parameters**	**-2LL**	**AIC**	**BIC**
Demographic (Baseline)				-462.16	10	924.32	944.326	984.633
Intercept	-0.056	0.049	0.250					
Slope	-0.005	0.002	0.004					
Demographic (T3)				-454.382	10	908.764	928.764	969.070
Intercept	-0.058	0.046	0.210					
Slope	-0.005	0.002	0.001					
Health (Baseline)				-436.258	10	872.516	892.516	932.048
Intercept	-0.069	0.034	0.042					
Slope	-0.004	0.001	0.000					
Health (T3)				-459.547	10	919.094	939.094	979.377
Intercept	-0.071	0.026	0.006					
Slope	-0.003	0.001	0.006					
Lifestyle (Baseline)				-451.680	10	903.36	923.361	963.250
Intercept	-0.252	0.111	0.023					
Slope	-0.006	0.004	0.101					
Lifestyle (T3)				-439.773	10	879.546	899.547	939.411
Intercept	-0.243	0.130	0.061					
Slope	-0.014	0.005	0.006					
Demographic + Health (Baseline)				-1794.123	14	3588.246	3616.245	3671.591
Intercept	-0.055	0.027	0.041					
Slope	-0.003	0.001	0.000					
Demographic + Health (T3)				-2033.306	14	4066.612	4094.613	4151.009
Intercept	-0.059	0.021	0.005					
Slope	-0.003	0.001	0.000					
Demographic + Health + Lifestyle (Baseline)				-2015.605	16	4031.21	4063.209	4125.997

Intercept	-0.059	0.026	0.024					
Slope	-0.003	0.001	0.000					
Demographic + Health + Lifestyle (T3)				-2181.492	16	4362.984	4394.983	4458.726
Intercept	-0.060	0.020	0.003					
Slope	-0.003	0.001	0.000					
Standard Genetic				-438.497	10	876.994	896.994	936.858
Intercept	-0.016	0.034	0.633					
Slope	-0.001	0.001	0.456					
AD Standard Genetic				-438.639	10	877.278	897.277	937.142
Intercept	0.005	0.041	0.896					
Slope	0.000	0.001	0.814					
APOE				-438.889	10	877.778	895.777	935.667
Intercept	0.135	0.129	0.297					
Slope	0.001	0.004	0.885					
Formative Genetic				-139.259	10	278.518	298.518	338.382
Intercept	1.139	0.039	0.000					
Slope	0.022	0.003	0.000					
AD Formative Genetic				-440.968	10	881.936	901.937	941.675
Intercept	0.117	0.063	0.064					
Slope	0.005	0.002	0.021					
Demographic + Health + Lifestyle + Standard Genetic (Baseline)				-398.512	10	797.024	817.024	855.717
Intercept	-0.040	0.022	0.072					
Slope	-0.002	0.001	0.003					
Demographic + Health + Lifestyle + Standard Genetic (T3)				-408.300	10	816.600	836.599	875.948
Intercept	-0.044	0.018	0.015					
Slope	-0.002	0.001	0.001					
Demographic + Health + Lifestyle + AD Standard Genetic (Baseline)				-398.966	10	797.932	817.931	856.624
Intercept	-0.036	0.024	0.133					
Slope	-0.002	0.001	0.006					

Demographic + Health + Lifestyle + AD Standard Genetic (T3)				-408.812	10	817.624	837.623	876.972
Intercept	-0.043	0.020	0.028					
Slope	-0.002	0.001	0.001					
Demographic + Health + Lifestyle + *APOE* (Baseline)				-397.010	10	794.02	814.019	852.740
Intercept	-0.048	0.027	0.076					
Slope	-0.003	0.001	0.001					
Demographic + Health + Lifestyle + *APOE* (T3)				-407.884	10	815.768	835.768	875.143
Intercept	-0.053	0.021	0.001					
Slope	-0.003	0.001	0.001					
Demographic + Health + Lifestyle + Formative Genetic (Baseline)				-386.776	10	773.552	793.552	832.245
Intercept	0.090	0.023	0.000					
Slope	0.000	0.001	0.865					
Demographic + Health + Lifestyle + Formative Genetic (T3)				-403.017	10	806.034	826.034	865.383
Intercept	0.055	0.023	0.016					
Slope	0.000	0.001	0.389					
Demographic + Health + Lifestyle + AD Formative Genetic (Baseline)				-404.335	10	808.670	828.670	867.221
Intercept	-0.039	0.023	0.088					
Slope	-0.002	0.001	0.003					
Demographic + Health + Lifestyle + AD Formative Genetic (T3)				-415.351	10	830.702	850.702	889.891
Intercept	-0.035	0.019	0.058					
Slope	-0.002	0.001	0.008					

Note. T3 = Time point 3; Est. = Regression Estimate; SE = Standard Error; H0 = Log Likelihood; -2LL = -2 Log Likelihood; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; ; *APOE = Apolipoprotein*; *CLU = Clusterin; CR1 = Complement receptor 1*; *PICALM = Phosphatidylinositol-binding clathrin assembly* protein; AD genetic risk includes *APOE, CLU, CR1, PICALM*.

Table 4-12

Study 1b (Research goal 3): Change in demographic, health, lifestyle, demographic + health + lifestyle + standard genetic, demographic + health + lifestyle + formative genetic risk scores from time point 1 to 3 on episodic memory performance and change

Risk Score	**Model Results**			**Model Fit Statistic**				
	Est.	**S.E.**	***p***	**H0 value**	**Free Parameters**	**-2LL**	**AIC**	**BIC**
Demographic (*n* = 414)				-460.199	10	920.398	940.398	980.656
Intercept	-0.036	0.078	0.645					
Slope	-0.005	0.003	0.092					
Health (*n* = 382)				-434.061	10	868.122	888.121	927.576
Intercept	-0.029	0.037	0.432					
Slope	0.001	0.001	0.598					
Lifestyle (*n* = 380)				-428.807	10	857.614	877.614	917.015
Intercept	0.027	0.134	0.840					
Slope	-0.006	0.004	0.129					
Demographic + Health + Lifestyle + Standard Genetic (*n* = 335)				-380.805	10	761.610	781.610	819.752
Intercept	-0.037	0.036	0.303					
Slope	-0.001	0.001	0.406					
Demographic + Health + Lifestyle + AD Standard Genetic (*n* = 335)				-380.805	10	761.610	781.610	819.752
Intercept	-0.037	0.036	0.303					
Slope	-0.001	0.001	0.406					
Demographic + Health + Lifestyle + *APOE* (*n* = 336)				-381.000	10	762.000	782.001	820.172
Intercept	-0.038	0.036	0.291					
Slope	-0.001	0.001	0.397					

Note. Est. = Regression Estimate; SE = Standard Error; H0 = Log Likelihood; -2LL = -2 Log Likelihood; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; *APOE = Apolipoprotein*; *CLU = Clusterin; CR1 = Complement receptor 1*; *PICALM = Phosphatidylinositol-binding clathrin assembly* protein; AD = Alzheimer's disease; AD standard genetic risk includes *APOE, CLU, CR1, PICALM*.

Table 4-13

Study 1b (Research goal 4): Area under the curve values for NA versus MCI status for independent and additive risk scores

Risk Index	**AUC**	**Standard Error**	**Asymptotic Significance**	**95% CI Interval**
Demographic	0.622*	0.035	0.001	0.554-0.690
Health	0.368*	0.037	0.003	0.295-0.441
Lifestyle	0.574	0.038	0.058	0.500-0.648
Standard genetic	0.566	0.040	0.080	0.488-0.643
AD Standard genetic	0.556	0.039	0.137	0.479-0.633
APOE	0.538	0.038	0.307	0.463-0.613
Demographic + Health	0.490	0.039	0.825	0.414-0.566
Demographic + Health + Lifestyle	0.558	0.045	0.193	0.471-0.646
Demographic + Health + Lifestyle + Standard genetic	0.512	0.046	0.812	0.421-0.603
Demographic + Health + Lifestyle + AD standard genetic	0.510	0.044	0.842	0.424-0.596
Demographic + Health + Lifestyle + *APOE*	0.520	0.045	0.671	0.433-0.608

Note. NA = Normal Aging; MCI = Mild Cognitive Impairment; AUC = Area Under Curve; CI = Confidence Interval; AD = Alzheimer's disease; *APOE = Apolipoprotein E.*

*$p<.05$

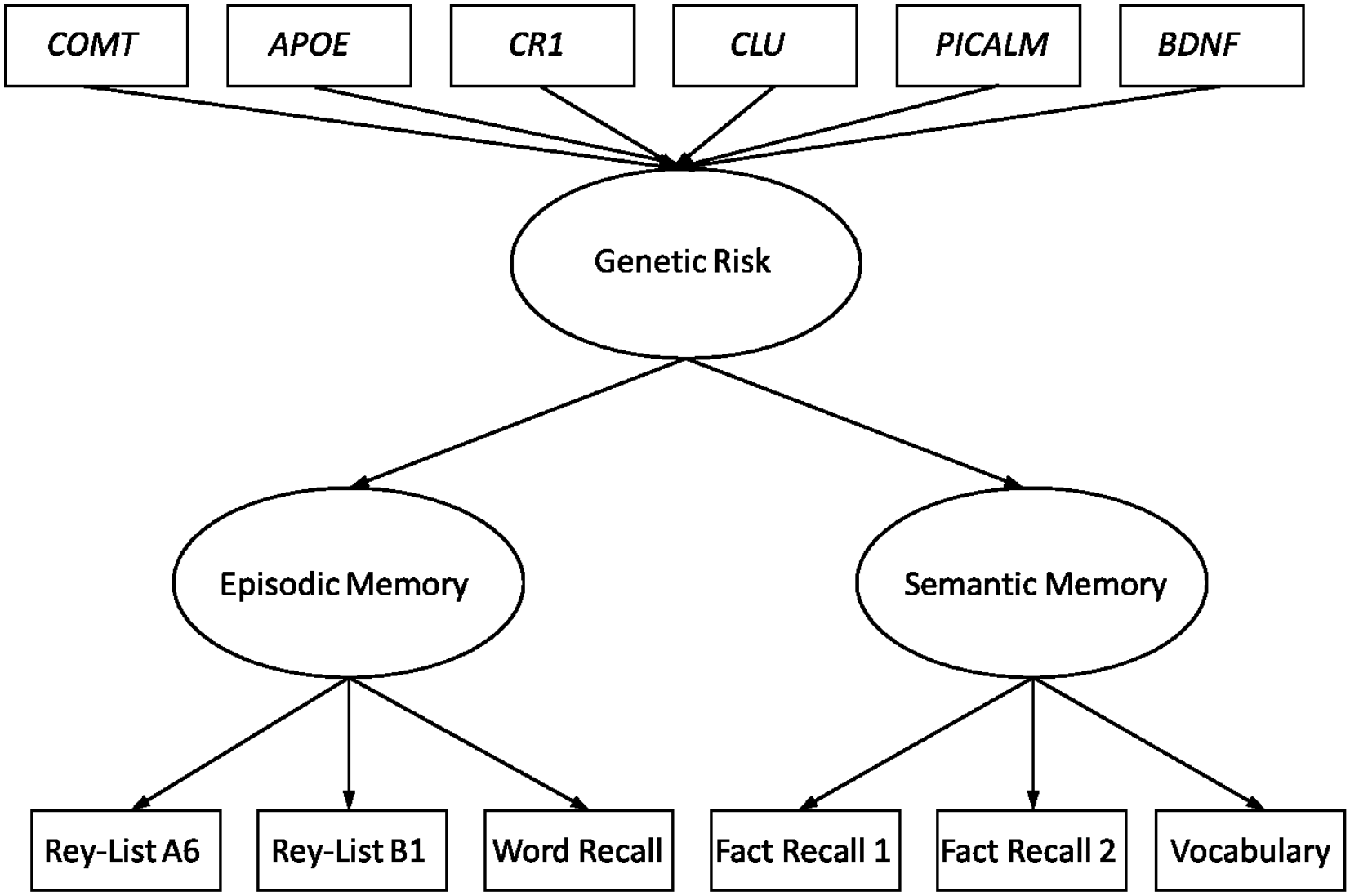

Figure 4-1. Conceptual model for formative composite genetic risk score using all six genetic polymorphisms. The model depicts the genetic risk factor score computed using two-factor episodic and semantic memory model.

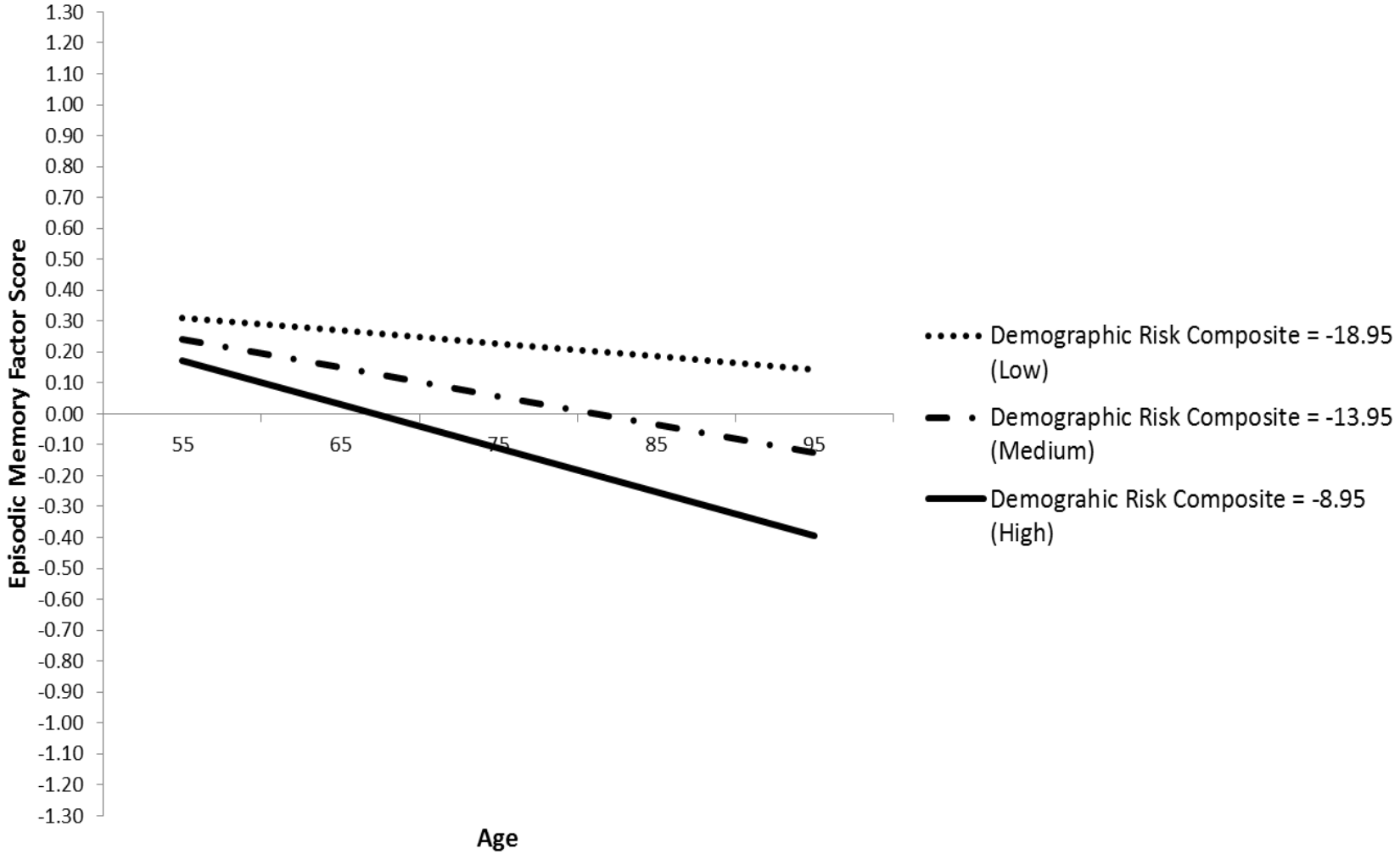

Figure 4-2. Predicted growth curve for episodic memory factor score using demographic risk score as a predictor with age centered at 75 years. High demographic risk score significantly predicted lower episodic memory at age 75 (p = .034) and steeper episodic memory decline (p = .034).

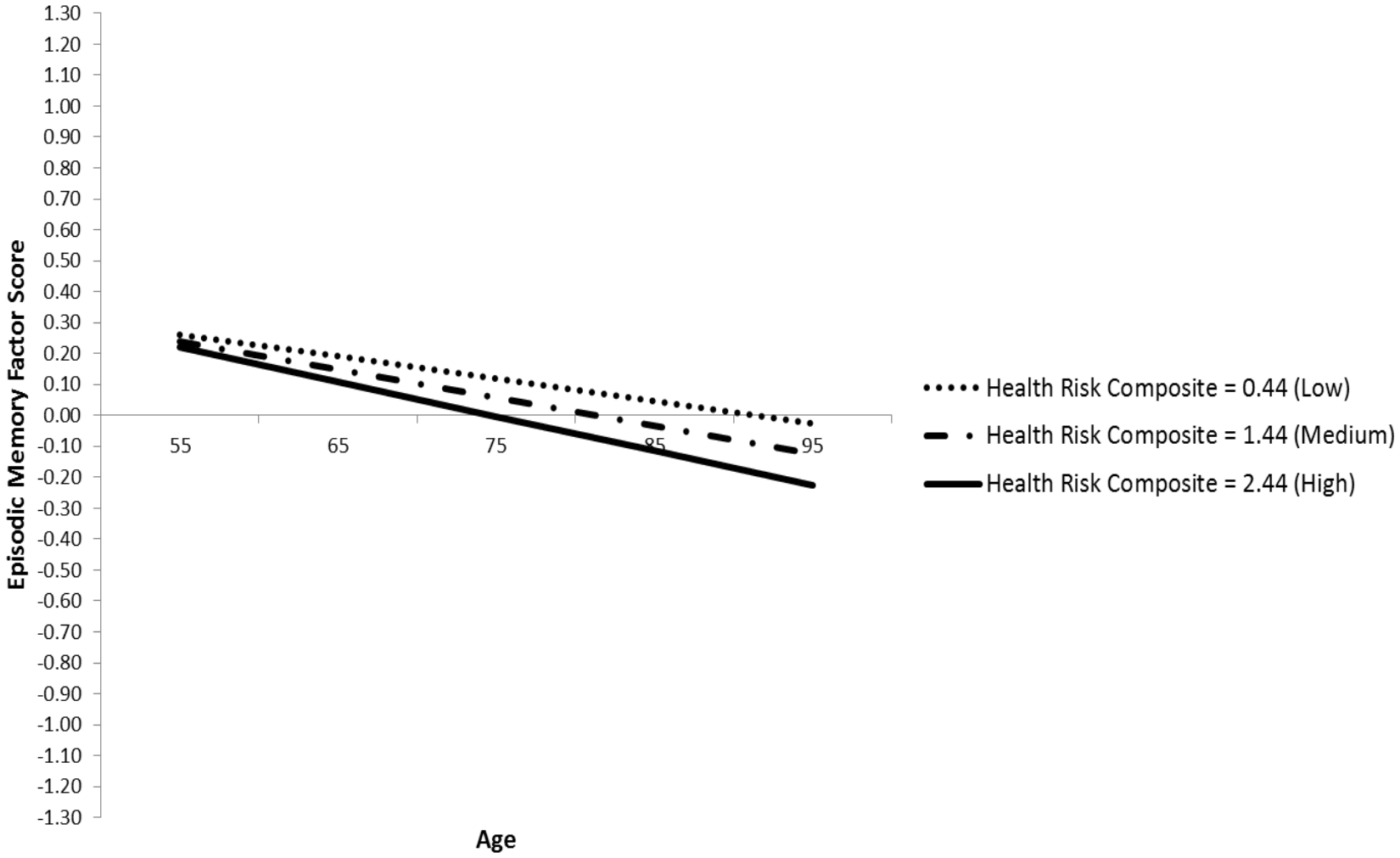

Figure 4-3. Predicted growth curve for episodic memory factor score using health risk score as a predictor with age centered at 75 years. High health risk score significantly predicted lower episodic memory at age 75 (p = .024) and steeper episodic memory decline (p = .003).

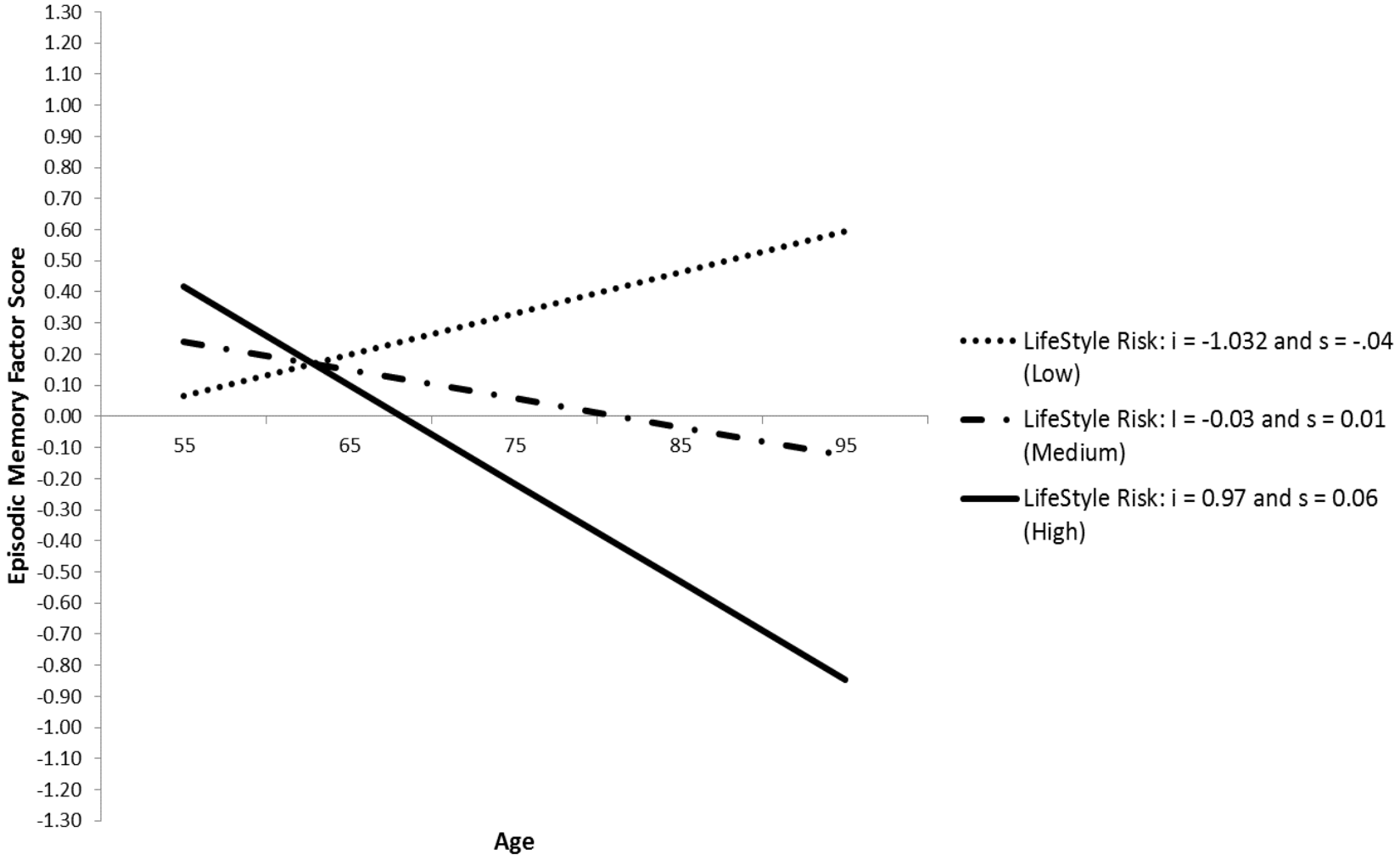

Figure 4-4. Predicted growth curve for episodic memory factor score using lifestyle risk score as a predictor with age centered at 75 years. High lifestyle risk score at age 75 years significantly predicted lower episodic memory at age 75 ($p < .001$) and change in lifestyle slope predicted steeper episodic memory decline ($p = .003$).

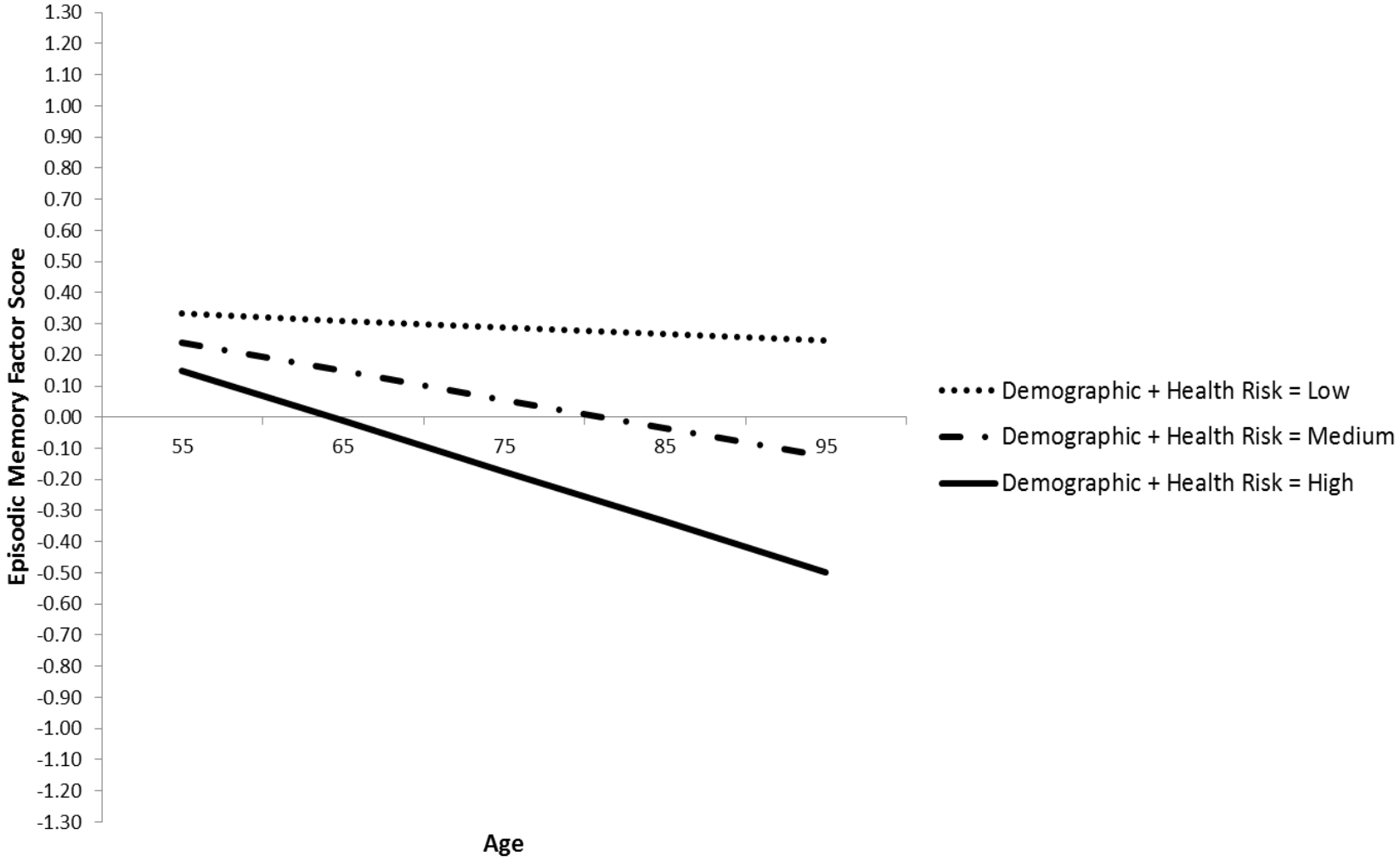

Figure 4-5. Predicted growth curve for episodic memory factor score using demographic + health risk score as a predictor with age centered at 75 years. Cumulative demographic + health risk score predicted lower episodic memory at age 75 and steeper decline.

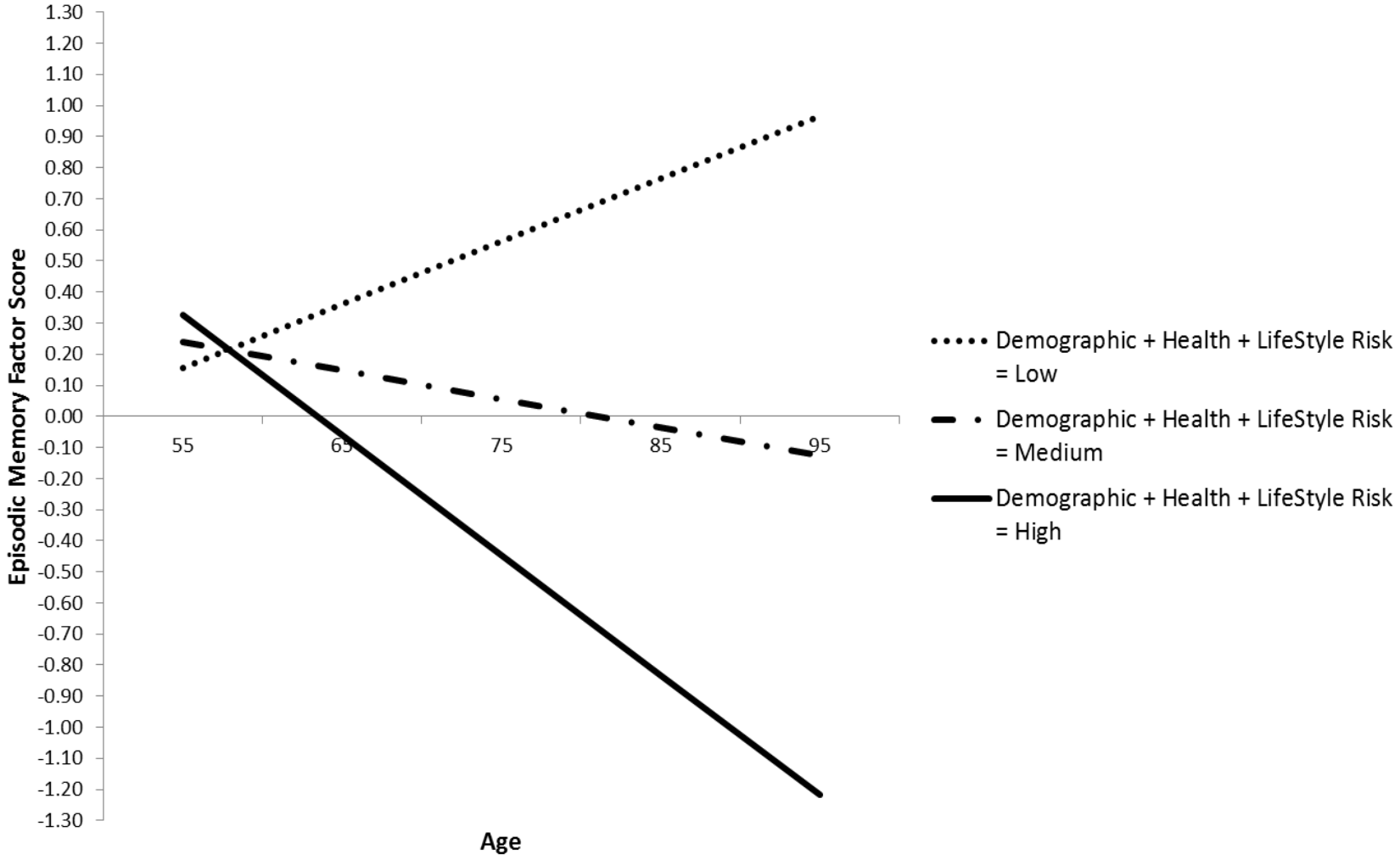

Figure 4-6. Predicted growth curve for episodic memory factor score using demographic + health + lifestyle risk score as a predictor with age centered at 75 years. Cumulative demographic + health + lifestyle risk score predicted lower episodic memory at age 75 and steeper decline.

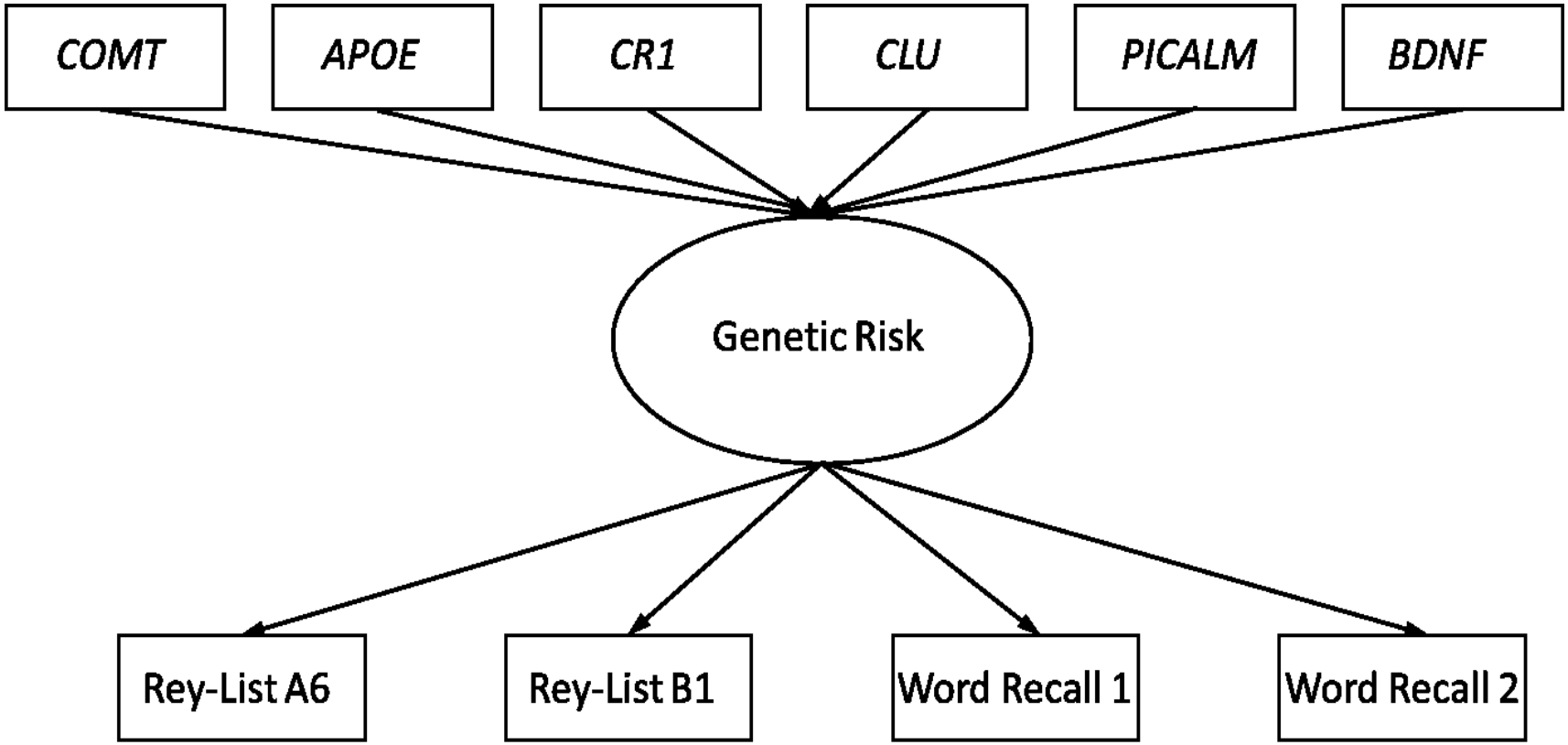

Figure 4-7. Final formative composite genetic risk score using all six genetic polymorphisms. The model depicts the genetic risk factor score computed using all four episodic memory indicators (Rey List A6, Rey List B1, Word Recall 1, Word Recall 2).

CHAPTER 5: STUDY 2

Synergistic associations of *Catechol-O-methyltransferase* and *Brain-derived neurotrophic factor* with executive function in aging are selective and modified by *Apolipoprotein E*

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1. Introduction

Genetic associations in complex and multifaceted neurocognitive phenotypes are known to be detectable but relatively small in magnitude. Such associations are likely to be polygenic, interactive, or combinatorial in influence. They operate through relevant neurobiological mechanisms, and vary in influence according to the match between endogenous factors and neurocognitive domain or clinical outcome status (Deary et al., 2004; Goldberg and Weinberger, 2004; Gomar et al., 2011; Green et al., 2008; McClearn, 2006). Recent advances in understanding relevant molecular genetics, neurophysiological mechanisms, and key structural and functional aspects of specific cognitive phenotypes have led to increasing attention to potential associations among dopaminergic and neurotrophic related genes expressed in the prefrontal cortex and influencing aging changes in executive functions (Bäckman et al., 2006; Harris and Deary, 2011; Savitz et al., 2006). Two polymorphisms have received sustained attention for their potential contributions to aging-related individual differences in executive function (EF): *Catechol-O-methyl transferase* (*COMT*; rs4680) and *Brain-derived neurotrophic factor* (*BDNF*; rs6265) (Bilder et al., 2004; Miyajima et al., 2008; Payton, 2009; Starr et al., 2007). The third polymorphism we consider is *Apolipoprotein E* (*APOE*; rs7412, rs429358). *APOE* has received considerable attention for both predictive and modifying roles in normal cognitive aging, Mild Cognitive Impairment (MCI), and Alzheimer's disease (AD) (Brainerd et al., 2011; Farlow et al., 2004; Harris and Deary, 2011; Kantarci et al., 2012; Saunders et al., 1993). In this study we examined both the independent, interactive, and additive effects of the first two polymorphisms on EF as well a subsequent potential vulnerability conveyed with effect modification by *APOE*-related cognitive risk.

EF is a complex neurocognitive phenotype that may vary with aging in terms of both latent structure and performance on manifest variables (Luszcz, 2011). Quantitative modeling and empirical results with younger adults, normal older adults, and clinical populations have confirmed that unidimensional (single-factor) solutions are typically observed in normal and clinical (impaired) aging (de Frias et al., 2009; McFall et al., 2013). We assembled two common markers (each) of EF inhibition (Hayling Sentence Completion, Stroop) and EF shifting (Brixton Spatial Anticipation, Color Trails). In order to avoid multiple significance tests and enhance the construct and measurement characteristics of these four manifest variables, we performed confirmatory factor analyses on the performance data, resulting in a replicated and validated latent variable representation of EF for non-demented older adults (de Frias et al., 2006).

Biological-to-neurocognitive rationales for exploring the *COMT* and *BDNF* SNPs in the context of EF are available (e.g., Erickson et al., 2008; Miyajima et al., 2008; Savitz et al., 2006; Starr et al., 2007). We summarize the most pertinent aspects of the proposed neural mechanisms as they are currently related to non-demented aging. The Val158Met *COMT* rs4680 polymorphism at codon 158 on chromosome 22q11 increases COMT enzymatic activity that in turn decreases dopamine levels particularly in the prefrontal cortex (Chen et al., 2004). This results in *COMT* homozygotes for the Met allele having greater dopamine levels than the Val allele homozygotes. Thus, non-demented older adults with any Val allele (Val-Val, Val-Met) may be at higher risk for EF impairment than those with the Met-Met combination (Nagel et al., 2008; Wishart et al., 2011). However, a variety of phenotypic associations have been observed for this polymorphism, with such characteristics linked to the tonic-phasic dopamine hypothesis (Bilder et al., 2004; Egan et al., 2001). Regarding BDNF, this factor is mainly present in the hippocampus and prefrontal cortex, and it may play a role in such phenotypes as episodic

memory, global cognitive functioning, and EF, perhaps interactively, additively, or differentially by age and gender (Komulainen et al., 2008; Raz et al., 2009; Savitz et al., 2006). Although not quite to the extent as *COMT*, this polymorphism has produced multiple phenotypic associations, likely due to variations in endogenous and environmental factors in the context of other relevant genes and measures of neurocognitive performance (Mandelman and Grigorenko, 2012).

Informed by overlapping neurobiological mechanisms and EF phenotypic expressions, but in the absence of a specific theory regarding the mechanisms of their potential synergistic associations, we recruited related theoretical perspectives linking them with non-demented aging. Specifically, an aging magnification or dynamic vulnerability perspective (e.g., Belsky et al., 2009; Fotuhi et al., 2009; Lindenberger et al., 2008) suggests that a combination of risk alleles from *BDNF* and *COMT* could effectively intensify the deleterious effects of brain aging on select neurocognitive phenotypes. We examined two ways of representing vulnerability effects in this study (Gomar et al., 2011; Harris et al., in press; McClearn, 2006). First, we examined interactive or multiplicative (e.g., gene x gene interactions, ending with gene x gene x age interactions) models to test moderating biological relationship between *COMT, BDNF*, and age. The genotype of each polymorphism was coded from 1-3 (3 = highest risk) and age was evaluated as a continuous variable. We reasoned that, if the interactive model would hold, adults with relatively non-risk (or even protective) alleles for either *COMT* or *BDNF* (or younger age) would be at a lower risk for cognitive decrements. Conceivably, removing even one risk factor could reduce some risk associated with either *COMT* or *BDNF* risk alleles, because at least one factor is moderating the others to produce the deleterious effect on EF. Second, as an alternative representation of genetic-plus-aging vulnerability, we performed parallel tests of additive effects. This additive model of genetic risk included subsets and the full following calculation, *COMT* +

BDNF + age. The additive model represents the notion that panels or combinations of risk biomarkers will influence cognitive phenotypic performance in normal aging and in early cognitive impairment (e.g., Gomar et al., 2011), even in the absence of independent or multiplicative associations. An additive model (Purcell et al., 2009; Harris et al., in press; Verhaaren et al., 2013) could indicate that a non-risk (or protective) allele for *BDNF* or *COMT* or younger age would effectively only eliminate the risk for one of the risk factors, but the risk associated with the other factors could still be present and influential. For convenience, we refer to both interactive and additive effects as synergistic associations with EF throughout the paper. For both biological and cognitive reasons, *BDNF* and *COMT* have been studied independently (rarely in addition or interaction) in the prefrontal cortex in non-demented older adults. For example, BDNF may interact with COMT levels in the prefrontal cortex through basal ganglia-thalamocortical loops (e.g., Alexander et al., 1986). Conceivably, decreases in the secretion of BDNF may be associated with normal cognitive decline and additional *COMT* effects may further regulate the effects of cognitive deficits. In the *BDNF* Val66Met polymorphism, *BDNF* Met homozygotes may be expected to produce selective cognitive deficits, as compared to *BDNF* Val homozygotes.

To our knowledge, the present additive effects model has not been reported for these two SNPs in neurocognitive aging (for other examples see Bertolino et al., 2006; Canli et al., 2008; McIntosh et al., 2013; Purcell et al., 2009; Verhaaren et al., 2013). However, independent and interaction effects of *COMT*, *BDNF*, and age have indicated suggestive results. For example, Wishart and colleagues (2011) examined a single EF test (Trail Making Test) and found COMT-EF effects in the expected direction and no *BDNF* x *COMT* interaction effect. However, in a follow-up analysis, adults with the combined risk alleles for *COMT* and *ANKK1* (*Ankyrin Repeat*

and Kinase domain containing 1) performed worst on the EF task. Regarding genetic vulnerability and aging, Nagel and colleagues (2008) examined the performance of younger and older groups on the Wisconsin Card Sorting Test (EF measure) as magnified by gene x gene interactions. For a younger group and an older group the deleterious effects of *COMT* Val carriers were visible in the older group of adults, and this was modulated by whether individuals were carriers of the *BDNF* Met allele. Other examples are appearing in related literatures (e.g., Gomar et al., 2011; McFall et al., 2014; Deshmukh et al., 2009).

The presence or absence of *COMT* and *BDNF* interactive and additive associations may be due to the moderating role of other unmeasured genetic variants. Therefore, to investigate whether an additional neurogenetic indicator of cognitive health and vulnerability might modulate the synergistic effect for EF performance, we examined effect modification by stratifying the groups by allelic risk for *APOE,* the most widely studied neurocognitive vulnerability gene in aging (Harris and Deary, 2011; Verghese et al., 2011). There are many studies with *APOE* risk and cognitive impairment (Small et al., 2004). The *APOE* genotype is involved in central nervous system repair and function, and is differentiated by three alleles: ε2, ε3, and ε4. The ε4 allele (both homozygosity and heterozygosity) is consistently linked to risk factors for cognitive aging decline, impairment, and dementia (Brainerd et al., 2011; Elias-Sonnenschein et al., 2011; Wisdom et al., 2011) in comparison to the ε2 allele, which has been found to be protective in numerous studies (Corder et al., 1994; de-Almada et al., 2011; Panza et al., 2000). The *APOE* gene has been reported to have an antagonistic pleiotropy effect, whereby the presence or absence of the ε4 allele may moderate the appearance of age differences (Jochemsen et al., 2012), as well as other grouping and modification effects (Edland et al., 2003; Niti et al., 2008; Risacher et al., 2013; Woodard et al., 2012). We investigated genetic and aging

effects as stratified by *APOE* allelic risk (i.e., the commonly implemented dichotomous comparison between risk (ε4+) group and no risk (ε4-) group) for a large sample of older adults.

We extend previous research by including a larger heterogeneous sample of well-characterized older adults, a wide band (40 years) of age within the sample, and an informative battery of four EF measures, including two tests each of shifting and inhibition, as represented by a quantitatively derived EF latent variable. Specifically, we tested independent, interactive, and additive effects pertaining to whether those with *COMT* risk alleles, *BDNF* risk alleles, and older age vulnerability performed worse on EF. Subsequently, we tested the effect modification by *APOE* allelic risk. Therefore, four research questions were examined. First, do carriers of the risk allele for *COMT* (Val+) and *BDNF* (Met+) perform worse on EF? Second, do either interactive (gene x gene) or additive (gene + gene) effects demonstrate synergistic associations, such that adults with combined risk alleles perform worse? Third, does age have an interactive or additive effect with *COMT*, *BDNF*, or both *COMT* and *BDNF*, such that older age magnifies the deleterious effect for genetic risk carriers? Fourth, do adults in *APOE* risk (ε4+) group perform more poorly than adults in the reduced *APOE* (ε4-) risk group for additive or interactive associations of *COMT, BDNF*, and age?

2. Method

2.1. Participants

This study uses recent data from the Victoria Longitudinal Study (VLS), a long-term project examining biomedical, health, and neurocognitive aspects of aging. General information on recruitment, methodological, and VLS characteristics are available elsewhere (e.g., Dixon and de Frias, 2004; Dolcos et al., 2012). All volunteers in the VLS were initially healthy, enrolled through advertisements, and received a small honorarium for their participation. The VLS and all

present data collection procedures are in full and certified compliance with prevailing human/institutional research ethics guidelines. Written informed consent was obtained from all participants. All participants were Caucasian with complete access to Canadian national health care. The present sample reflects the implementation of exclusionary criteria affecting individuals with (a) diagnosis or history of dementia, (b) anti-psychotic medication, (c) Mini Mental State Exam scores less than 24, (d) uncontrolled hypertension, (e) insulin-controlled diabetes, and (f) history of serious head injury (e.g., hospitalized). Accordingly, $n = 634$ participants (age range = 53-95, mean age = 70.58 (SD = 8.65)) including 423 females and 211 males with genetic data were included.

2.2. DNA Extraction and Genotyping

Saliva was collected according to standard procedures from Oragene DNA Genotek and stored at room temperature in Oragene® disks until DNA extraction. DNA was manually extracted from 0.8 ml of saliva sample mix using the manufacturer's protocol with adjusted reagent volumes. Genotyping was carried out by using a PCR-RFLP strategy to analyze the allele status for *BDNF* (rs6265), *COMT* (rs4680), and (*APOE*; rs7412, rs429358). Genotyping was successful for the targeted SNPs for all present participants. Table 5-1 presents participant characteristics and allele frequency by genotype for *BDNF*, *COMT,* and *APOE*. The genotype frequencies for the three examined genotypes did not differ significantly from Hardy-Weinberg equilibrium: *BDNF* rs6265 ($\chi^2 = 0.837$, $p = 0.36$), *COMT* rs4680 ($\chi^2 = 2.786$, $p = 0.10$), and *APOE* rs7412, rs429358 ($\chi^2 = 0.545$, $p = 0.909$) or among any baseline characteristics. For purposes of analyses we included all three allelic combinations for *COMT* and *BDNF* (Met/Met, Met/Val, and Val/Val). For evaluating modification by *APOE*, we deleted all ε2/ε4 carriers and then compared patterns between ε4+ carriers and ε4- carriers.

2.3. Executive Function Measures

Two dimensions of EF (inhibition, shifting) were each measured by two standard and frequently used tests for both behavioral and clinical studies in older adults (for details see: de Frias et al., 2006, 2009; McFall et al., 2013, 2014).

2.3.1. Hayling Sentence Completion (Hayling; Inhibition)

The test consists of two sections, each comprising fifteen sentences. In the first section, participants must state the last word that correctly completes the sentence. In the second section, the participants must say a word that is not at all related to the sentence. The standardized scores are based on an error score from the first section and the speed of each response from both sections, which are then combined to obtain the final score (1 = impaired to 10 = superior).

2.3.2. Stroop (Inhibition)

The test consists of three parts. In part A, participants are asked to name four different colors that appear as 24 dots in six different rows. In part B, the same colors appear but are printed as common words. In part C, each color is represented as a textual representation with different colored ink. The participants are measured based on latencies. The final score is the standardized Stroop interference index ([Part C- Part A]/ Part A), with a lower index reflecting better performance.

2.3.3. Brixton Spatial Anticipation (Brixton; Shifting)

The test consists of 10 different circles; one being blue while the rest are colorless. The circles appear in a 56-page booklet. The blue colored circle shifts position with some logical pattern after each page. This test measures the mechanism of shifting by asking participants to guess where the blue colored circle will appear on the next page. The total number of incorrect guesses are measured and the final scores are calculated (1 = impaired to 10 = superior).

2.3.4. Color Trails (Shifting)

This test comprises two different tasks in which participants connect different attributes, such as numbered and colored circles. In the first section, participants connect numbers from 1–25 within circles that are randomly organized on a page. In the second section, they connect the numbers in order but alternating between pink and yellow circles. Errors and latency scores are then computed to obtain the standard overall score.

2.4. Statistical Analysis

Structural equation modeling (SEM) was used to analyze all research questions (i.e., Mplus 7; Muthén & Muthén, 1998-2012). All missing values for cognitive measures were assumed to be missing at random and handled using maximum likelihood. Missing predictor values were handled using list-wise deletion in Mplus. Only two participants with missing measures on all four EF tasks were lost due to list-wise deletion.

To test and establish a latent variable for EF, we used confirmatory factor analysis (CFA) to examine loadings of all four manifest variables (Stroop, Hayling, Brixton, and Color trails) on the predicted latent variable. The first model tested all observed variables on one latent EF factor. The best fitting model was determined by examining several fit statistics. The chi-square test of model (χ^2; $p > .05$) allowed for an overall indication of good model fit. Additional absolute/comparative fit indices were also examined to determine a good model fit to the data (Kline, 2011): the root mean square error of approximation (RMSEA $\leq .05$), comparative fix index (CFI $\geq .95$), and the standardized root mean square residual (SRMR $\leq .08$). The one-factor parsimonious model provided good fit to the data and was used as the final CFA model for EF. Unstandardized regression coefficients for the expected EF latent variable were examined to determine higher or lower performance.

For each research question, we used multiple linear regression models (within Mplus 7). Our specific analyses are described below in the following convention. EF was regressed on all predictors simultaneously for all models. The interaction terms were calculated as product variables (gene x gene and gene x gene x age). The additive terms were calculated as sums of risk by adding the allelic risk (coded from 1-3 with three being the highest risk) and chronological age. Higher score represented higher genetic risk and older age. When testing for additive effects, only predictors absent from the additive term were added to covary for any remaining independent effects. For interactive effects, all three predictors (*COMT*, *BDNF*, and age) were always entered in the interactive model to covary for any independent effects. On the basis of two preliminary analyses, we did not include gender as a covariate. First, our tests of gender effects in allelic distributions for all three genotypes (*APOE*, *BDNF*, *COMT*) were not significant (see Table 5-1). Second, our test of gender differences in EF performance both overall and by each allelic group (within the three SNPs) also produced non-significant effects. We constrained our analysis plan to include the essential 13 models. By using the EF latent variable and testing only specific hypotheses, we set statistical significance threshold at $p < .05$.

For research question one, EF was regressed on *COMT, BDNF*, and age. Two models were tested for interaction and additive effects for research question two. Specifically, EF was simultaneously regressed on (a) *COMT* x *BDNF*, *COMT, BDNF*, age, and (b) *COMT* + *BDNF*, age. For research question three, six models were tested for interactive and additive effects with age. For interactive associations, EF was simultaneously regressed on (a) *COMT, BDNF*, age, *COMT* x age, (b) *COMT, BDNF*, age, *BDNF* x age, and (c) *COMT, BDNF*, age, *COMT* x *BDNF* x age. For additive effects, EF was regressed on (a) *BDNF, COMT* + age, (b) *COMT, BDNF* + age, (c) *COMT* + *BDNF* + age. For research question four, we first deleted all ε2/ε4 carriers (*n* =

30) and then stratified the groups by *APOE* risk (ε4+) versus reduced risk (ε4-) subgroups. Four models were then examined for interactive and additive effects by each subgroup, where EF was simultaneously regressed on (a) *COMT, BDNF*, age, *COMT* x *BDNF* x age and (b) *COMT* + *BDNF* + age.

3. Results

Descriptive characteristics by *COMT*, *BDNF*, and *APOE* alleles are displayed in Table 5-1. The best CFA model for EF was obtained with the one factor latent variable, which provided the best fit for all four EF tasks (χ^2 (*df*) = 3.011 (2), $p = 0.222$; RMSEA (confidence interval) = 0.028 (0.000-0.089); CFI = 0.993; SRMR = 0.015). This latent variable was used in the analyses for all four research questions. Regarding the first research question, we observed that neither *COMT* (β = 0.114; standard error (SE) = 0.103; $p = 0.271$) nor *BDNF* (β = 0.101; SE = 0.124; $p = 0.415$) significantly predicted EF performance. However, as expected, a one-unit increase in age was associated with a significant decrease (β = -0.134; SE = 0.016; $p < .001$) on EF performance.

Regarding the second research question, neither the *COMT* x *BDNF* interaction (β = 0.046; SE = 0.178; $p = 0.795$) nor the *COMT* + *BDNF* (β = 0.109; SE = 0.079; $p = 0.169$) additive effects model significantly predicted EF performance. Regarding the third research question, only age significantly predicted poorer EF performance in all three interactive models (see Table 5-2, rows 4, 8, 12 under research question three (interactive)). However, all three models examining additive effects with age significantly predicted EF performance in the expected direction. Specifically, a one-unit increase for additive effects of both *COMT* + age (β = -0.132; SE = 0.015; $p < .001$) and *BDNF* + age (β = -0.132; SE = 0.015; $p < .001$) predicted poorer EF performance (see Table 5-2, rows 1-4 under research question three (additive)).

Moreover, the three-way model produced a one-unit increase in the additive effect, for which *COMT* + *BDNF* + age significantly predicted lower EF performance (β = -0.129; SE = 0.015; $p < .001$) (see Table 5-2, row 5 under research question three [additive]).

Regarding the fourth research question, the *COMT* x *BDNF* x age interactive effect did not significantly predict EF performance as stratified by *APOE* allelic risk (ε4+) group (β = 0.005; SE = 0.005; $p = .285$) and reduced risk (ε4-) group (β = -0.004; SE = 0.003; $p = .173$). However, the corresponding three-way *COMT* + *BDNF* + age additive effect model significantly predicted EF performance as stratified by *APOE* groups. Although the difference between the *APOE* risk and reduced risk group was not significantly different (β = -0.039; SE = 0.165; $p = .811$), we observed slightly lower EF performance in the *APOE* risk (ε4+) group (β = -0.136; SE = 0.024; $p < .001$) than in the reduced *APOE* risk (ε4-) group (β = -0.131; SE = 0.020; $p < .001$).

We then conducted a post hoc analysis to check the extent to which the age variable influenced the 3-way additive effect on EF. We dichotomized the sample into young-old (YO) (< 70 years old; $n = 296$) and old-old (OO) (≥ 70 years old; $n = 338$) groups. Arguably, if age was driving this effect on EF then we should expect to see similar patterns in both groups. Instead, we observed different patterns. Whereas in the YO group, the *COMT* + *BDNF* + age effect on EF was not significant (β = 0.013.; SE = 0.008; $p = .089$), in the OO group the additive model was significant and in the expected direction (adults with additive allelic risk plus old age showed poorer performance) (β = -0.151; SE = 0.026; $p < .001$). The additive synergistic effects appear across a 40-year band of aging and are especially magnified with aging.

4. Discussion

We tested independent, interactive, and additive associations of *COMT* and *BDNF* risk alleles, along with age and effect modification by *APOE* allelic risk, in executive functioning for a large sample of normal older adults. Previous studies have reported results supportive of an interactive (Nagel et al., 2008) and additive (McIntosh et al., 2013 with schizophrenia related polymorphisms and cognition) aging-related magnification or intensification hypotheses (Fotuhi et al., 2009; Lindenberger et al., 2008; McClearn, 2006). It was unknown how model-specific (interactive or additive) or generalizable these effects would be across samples, ages, and dimensions of executive functioning. For the present study, results consistent with this general hypothesis would be produced through interactive or additive gene risk (with synergistic effects of risk alleles associated with poorer performance) or age plus gene risk (with older age differences in genetic-cognition associations).

We observed a consistent age effect for a latent variable representing EF performance, as would be expected in the literature (de Frias et al., 2006; Luszcz, 2011). Although expected, this established at the outset the important precondition for age-specific genetic vulnerability hypotheses. Our sample featured a continuous 40-year band of older adults, thus testing genetic vulnerability for *COMT*, *BDNF*, and *APOE* within older adulthood and complementing the typically examined extreme group comparisons of young and old adults. In addition, the confirmed EF latent variable offers a more robust representation of EF than is typically available in single-indicator studies (Wishart et al., 2011), most of which employ different and single EF tests. The latent variable approach reduces the number of models tested and groups the shared variance among all EF tests. In addition, relatively few examples of genetic association studies have been conducted with multiple indicator latent variable representations (McFall et al., 2014).

Given that age confers some vulnerability in EF, the next issue was whether the two polymorphisms were associated with EF. Notably, however, no corresponding independent associations with EF were observed for either the *BDNF* or *COMT* polymorphisms for our first research question. Therefore, we continued to test the two key aspects of this study, examining the two renditions of genetic and age risk that could convey cognitive vulnerability in normal older adults. Regarding the second research question, we found no interactive or additive associations with *COMT* and *BDNF* risk alleles on EF performance. From this perspective, there was no evidence of magnification effects of either genetic risk factor.

For our third research question, we observed systematically different results for the interactive versus additive models. Notably, only the additive model produced significant vulnerability associations with EF performance. Specifically, the additive associations with EF for *COMT* + age, *BDNF* + age, and *COMT* + *BDNF* + age were all significant. In contrast, the corresponding interactive models were not significant. The main evidence favoring the additive version of risk vulnerability and its potential for demonstrating associations with cognitive phenotypes in non-demented older adults was the three-way synergistic effect. This result showed exacerbated deficits for the vulnerability components of the allelic combinations, as they operated in a complementary and additive way that was associated with poorer EF performance. Arguably, this result pertains to general magnification or intensification hypotheses, extending earlier research with different polymorphisms and cognition (e.g., McIntosh et al., 2013; Verhaaren et al., 2013). In contrast to the not significant interaction effects, the small but significant additive effects remain neurobiologically interesting. Arguably, not significant traditional interaction effects may mask different mechanisms through which synergies can be transmitted (e.g., additive pathways and vulnerabilities of biomarker influence where eliminating

one risk factor will not reduce the risk associated with other risk factors). Both models of synergistic biomarker effects should continue to be studied. In addition, we note that the present study included adults along a continuous 40-year age range. This suggests that even within older adulthood, advancing chronological age may be an index along which researchers could detect evidence of increasing modulation of genetic, neurobiological, and environmental associations with neurocognitive functioning. The post hoc age-comparative analyses clarified these results. Whereas we observed no 3-way additive effect in the young-old group, the full significant additive effect was observed in the old-old group. Notably, the additive allelic risk for *COMT* and *BDNF* with very old age was associated with poorer EF performance. This implies that even within older adulthood chronological age is important and substantial in its influence on EF performance, but additive synergistic associations may be further magnified in very old adults. In terms of mechanisms, the additive model suggests that having only one protective factor (e.g., *COMT;* Met/Met allele) only reduces the risk associated with *COMT*, but does not affect the risk associated with *BDNF* risk allele or biological aging. In contrast, interactive effects (not observed here) may suggest that the moderation of *BDNF* risk allele factor on EF by *COMT* protective factor may dilute the risk associated with *BDNF* allelic risk. These results and the extant literature, however, do not yet provide specific guidance regarding the neurobiological underpinnings of these complex magnification effects (Harris et al., in press; Lindenberger et al., 2008; Savitz et al., 2006).

The role of aging in presumed aging-genetic magnification of neurocognitive deficits and impairment deserves further attention. Clearly, chronological age (and especially age groups) is not a causal factor but instead a proxy for to-be-determined underlying biological changes indexed by, but not tantamount to, age (MacDonald et al., 2011; Nakumura and Miyao, 2007).

As theoretical and measurement advances continue, such concepts as biological vitality or biological age (e.g., Anstey, 2008; MacDonald et al., 2004) may enhance future efforts to examine aging-related vulnerability and magnification effects in the context of genetic polymorphisms, about which the underlying molecular mechanisms are becoming better understood. Systematic but unmeasured biological or health influences—indexed imperfectly by chronological aging—may be among the reasons that inconsistent associations have been observed for single candidate-gene links (including *BDNF* and *COMT*) with various cognitive phenotypes in older adults (Deary et al., 2004; Fotuhi et al., 2009; Mandelman and Grigorenko, 2012). Relatively recent literature reporting early tests of polygenic effects is small (but growing) and promising (but not yet strong)—and this too may benefit from stronger representation of biological aging. The present study is the first to examine additive effect models for genetic polymorphism associated with cognitive decline and impairment and it may therefore serve as a model for future studies testing additive effects. The approach and initial results have substantial promise for the development of panels of biomarker influences in non-demented aging.

For our fourth research question, we analyzed the *APOE* risk (ε4+) and reduced risk (ε4-) groups separately, with the expectation that we would observe a version of an antagonistic pleiotropy effect. Although not significant, we observed slightly lower EF performance for *APOE* risk (ε4+) group than the reduced risk (ε4-) group for additive effects of *COMT, BDNF*, and age. The potential magnification of *COMT* and *BDNF* allelic risk may be especially detectable and active in the context of older adults who are carriers of the most prominent neurogenetic risk factor for cognitive decline. In the context of the powerful *APOE* (*ε4+*) risk factor among non-demented older adults, the additional risk provided by *COMT* and *BDNF* risk alleles may be more easily or differentially detectable. We note that older adults in the absence

of the *APOE* (ε4+) risk factor may also be at risk for cognitive impairment from other risk factors in old age (e.g., stress, physical activity; see Fotuhi et al., 2009). In addition, individuals with allelic risk may not develop cognitive decline in old age (Henderson et al., 1995) or their allelic risk may be exacerbated in combination with other diseases or factors (i.e., cardiovascular disease; see Kang et al., 2005). As a follow-up, we tested the effect of *APOE* alone without separating the ε4+ and ε4- groups. The significant effect modification showed an effect size of -0.007. This implies that although the effect modification between the groups are not significantly different in value, the risk and reduced risk groups must be separated to observe the large effect modification present in an additive vulnerability model for genetic and age on EF. Future research may investigate the magnification hypothesis not only among genetic variants with known neurobiological underpinnings for specific cognitive phenotypes, but also in the context of prominent neurodegenerative-related or vulnerability genetic variants (especially *APOE*) with larger samples of ε4+ carriers. However, other neurobiological factors and genetic variants related to age are emerging in the literature. These include the afore-mentioned *ANKK1* (Wishart et al., 2011), several dopaminergic-related genes (e.g., Bellander et al., 2011), and insulin-related genes (e.g., McFall et al., 2013), as well as markers of aging-related brain resources (e.g., Lindenberger et al., 2008), emerging neurodegenerative conditions (e.g., MCI or Alzheimer's disease; Brainerd et al., 2011; Dixon et al., 2014; Dolcos et al., 2012), or aging-related health conditions with less proximal neurological implications (e.g., diabetes; Seaquist et al., 2012). In all cases, however, advances will be made with both substantial cross-sectional studies and emerging longitudinal or epidemiological studies.

Several strengths and limitations of the present study should be mentioned. First, although this study had no younger adult comparison group, it did feature a large sample of older

adults representing a broad (40-year) band of age (from age 53-95 years). Given the heterogeneity of typical aging, this characteristic provided a unique opportunity to investigate a within-age genetic risk intensification hypothesis. This provided a conservative and unique test of the application of the phenomenon with this wide age range. Second, the tests used to measure EF phenotypes were four standard neuropsychological measures that contributed to a latent variable. The latent variable approach provides protection for shortcomings of single-test approaches and is preferred over typical composite variable formulations, thus extending knowledge of genetic associations with EF. Third, given some emerging research, other genetic variants, gender differences (e.g., Altmann et al., 2014), and neurobiological sources of vulnerability (e.g., vascular risk factors such as hypertension) should be considered in the future. Although this study investigated a range of EF phenotypes, further research could include additional domains such as neurocognitive speed and memory. For example, given the BDNF-hippocampus link and *APOE* and memory/AD risk, future research may examine *BDNF* allelic risk and *APOE* effect modification hypothesis for at least episodic memory, if not semantic and working memory (Mandelman and Grigorenko, 2012). Fourth, cross-sectional studies have well-known limitations in interpreting mechanisms and differences. Although these limitations apply to the present study, the wide age range offers new and valuable information. Certainly, longitudinal studies of these phenomena are encouraged. Fifth, in our effort to explore the aging magnification hypothesis, we examined 13 regression models because of our clear and specific vulnerability hypotheses and our approach of using an EF latent variable, we set the statistical significance standard to $p < .05$. Our decision was informed by the expectation of subtle magnification effects within age (as compared with group designs) and specific interest in comparing two versions of vulnerability models.

In sum, genetic associations with complex cognitive phenotypes may confer exacerbated risk in selective polygenic (interactive and additive) combinations. We examined independent, additive, and interactive effects of *COMT* and *BDNF* alone and as stratified by *APOE* groups. Consistent with the specific expectations, we observed a synergistic effect (*BDNF* + *COMT* + Age) for EF performance, but selectively for the additive models. We note as an issue for future research that the overall and cognitive health of the present sample may be partly responsible for the systematically differential results between the two representations of magnified genetic-aging vulnerability. Future research can investigate the applicability of the interactive model for different phenotypes and samples (e.g., cognitively impaired). Nevertheless, as noted by recent observers, approaching the neurogenetics of normal aging from the perspective that incorporates independent, synergistic, and modifying risk (or protection) factors may yield further understanding of the cognitive neurobiology of aging.

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Disclosure Statement

All authors confirm that there is no actual or potential conflict of interest. All research has been approved continuously by relevant institutional review boards. Certificates are available and on file in the University of Alberta Research Services Office and the US National Institutes of Health. All participants have completed and signed informed consent forms.

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Table 5- 1

Participant characteristics by genotype

	COMT				***BDNF***				***APOE***		
Characteristics	**Met/Met**	**Met/Val**	**Val/Val**	***p*[a]**	**Met/Met**	**Met/Val**	**Val/Val**	***p*[a]**	**ε4-**	**ε4+**	***p*[a]**
n	146	338	150	--	27	189	418	--	455	149	--
Age (years)	70.15 (8.86)	70.85 (8.68)	70.40 (8.439	0.69	68.54 (6.32)	71.45 (8.52)	70.32 (8.81)	0.15	70.90 (8.83)	69.86 (8.27)	0.20
Gender (F/M)	101/45	226/112	96/54	0.64	18/9	128/61	277/141	0.94	305/150	93/56	0.30
Education (years)	14.92 (3.11)	15.35 (2.80)	15.36 (3.15)	0.30	15.72 (2.70)	15.13 (2.99)	15.28 (2.96)	0.59	15.19 (2.95)	15.55 (3.07)	0.20
MMSE	28.72 (1.20)	28.72 (1.20)	28.56 (1.32)	0.40	29.15 (0.77)	28.74 (1.15)	28.62 (1.28)	0.07	28.66 (1.24)	28.68 (1.25)	0.89
Absolute Health	1.87 (0.74)	1.83 (0.74)	1.77 (0.77)	0.47	1.89 (0.80)	1.84 (0.72)	1.82 (0.75)	0.86	1.88 (0.73)	1.68 (0.77)	0.01
Relative Health	1.60 (0.66)	1.62 (0.72)	1.53 (0.71)	0.42	1.41 (0.69)	1.64 (0.69)	1.59 (0.71)	0.26	1.61 (0.70)	1.56 (0.73)	0.43
BP (mmHg) (S/D)	128.45/ 75.83	127.47/ 75.57	125.03/ 74.76	0.38/ 0.88	128.68/ 78.93	127.29/ 74.11	126.93/ 75.79	0.91/ 0.40	127.10/ 75.52	127.08/ 75.48	0.99/ 0.98
Bradburn Scale	3.05 (1.88)	3.26 (1.71)	3.23 (1.82)	0.47	3.44 (1.12)	3.06 (1.92)	3.26 (1.74)	0.37	3.21 (1.79)	3.26 (1.81)	0.76
Physical activities	15.26 (5.07)	15.90 (5.19)	15.93 (5.09)	0.41	16.37 (4.18)	15.73 (5.20)	15.73 (5.18)	0.82	15.60 (5.20)	16.13 (5.15)	0.28
Social activities	22.62 (6.67)	22.59 (6.78)	22.26 (6.84)	0.87	22.26 (7.32)	22.95 (6.72)	22.33 (6.75)	0.57	22.76 (6.61)	21.85 (7.16)	0.16
Integrative	19.70	18.87	18.78	0.59	19.00	17.72	19.64	0.05	18.71	20.20	0.08

Information	(9.77)	(8.38)	(9.26)	(6.45)	(8.54)	(9.18)	(8.56)	(9.25)

Key: *APOE*, *Apolipoprotein E; BDNF, Brain-derived neurotrophic factor*; BP, Blood pressure; Bradburn scale, Bradburn affect balance scale; *COMT*, *Catechol-O-methyl transferase;* MMSE, Mini-mental State Exam; *n*, total number; S/D, Systolic/Diastolic. Standard deviations are in parentheses. Absolute health represents self-rating to a perfect state of health, and relative health is rated with respect to others ones' own age, both based on a 1-5 scale (1 = very good, 5 = very poor). For the analyses involving the *APOE* genotypes, the ε2/ε4 carriers ($n = 30$) were deleted from the sample.

[a] $p < .0$

Table 5- 2

Unstandardized regression coefficients and model fit indices by research question for all models examined on executive function

				Model Fit Indicators			
Models	**β**	**SE**	***p***	**$\chi^2_M(df_M)$**	**CFI**	**RMSEA (90% CI)**	**SRMR**
Research question one							
(a) *COMT*	0.114	0.103	0.271	20.83 (11); $p = 0.035$	0.974	0.038 (0.010-0.062)	0.026
BDNF	0.101	0.124	0.415				
Age	-0.134	0.016	0.000				
Research question two							
(a) *COMT* + *BDNF*	0.109	0.079	0.169	20.08 (8); $p = 0.010$	0.968	0.049 (0.022-0.076)	0.029
Age	-0.134	0.016	0.000				
(b) *COMT* x *BDNF*	0.046	0.178	0.795	25.04 (14); $p = 0.034$	0.970	0.035 (0.010-0.057)	0.030
COMT	0.049	0.268	0.854				
BDNF	0.007	0.381	0.985				
Age	-0.134	0.016	0.000				
Research question three							
Interactive							
(a) *COMT* x age	0.006	0.012	0.593	22.00 (14); $p = 0.079$	0.978	0.030 (0.000-0.053)	0.028
BDNF	0.102	0.124	0.412				
COMT	-0.333	0.843	0.693				
Age	-0.147	0.029	0.000				
(b) *BDNF* x age	-0.016	0.016	0.319	24.62 (14); $p = 0.039$	0.971	0.035 (0.008-0.057)	0.026
COMT	0.112	0.104	0.281				
BDNF	1.193	1.103	0.279				
Age	-0.114	0.025	0.000				
(c) *COMT* x *BDNF* x age	0.000	0.002	0.909	26.03 (14); $p = 0.026$	0.968	0.037 (0.013-0.059)	0.030
COMT	0.140	0.249	0.575				
BDNF	0.139	0.353	0.694				
Age	-0.134	0.017	0.000				
Additive							
(a) *COMT* + age	-0.132	0.015	0.000	12.54 (8); $p = 0.129$	0.987	0.030 (0.000-0.060)	0.023

BDNF	0.105	0.123	0.396				
(b) *BDNF* + age	-0.132	0.015	0.000	17.66 (8); $p = 0.024$	0.974	0.044 (0.015-0.072)	0.027
COMT	0.116	0.103	0.259				
(c) *COMT* + *BDNF* + age	-0.129	0.015	0.000	9.24 (5); $p = 0.100$	0.988	0.037 (0.000-0.073)	0.022
Research question four							
***APOE*^{c} (ε4+)**							
(a) *COMT* x *BDNF* x age	0.005	0.005	0.285	53.98 (31); $p = 0.007$	0.939	0.050 (0.026-0.071)	0.046
COMT	-0.474	0.502	0.346				
BDNF	-0.628	0.675	0.352				
Age	-0.154	0.030	0.000				
(b) *COMT* + *BDNF* + age	-0.136	0.024	0.000	18.54 (13); $p = 0.138$	0.984	0.038 (0.000-0.073)	0.044
***APOE*^{c} (ε4-)**							
(i) *COMT* x *BDNF* x age	-0.004	0.003	0.173	53.98 (31); $p = 0.007$	0.939	0.050 (0.026-0.071)	0.046
COMT	0.554	0.318	0.081				
BDNF	0.671	0.453	0.139				
Age	-0.127	0.022	0.000				
(ii) *COMT* + *BDNF* + age	-0.131	0.020	0.000	18.54 (13); $p = 0.138$	0.984	0.038 (0.000-0.073)	0.044

Key: *APOE*: *Apolipoprotein E*; β, regression coefficient; SE, standard error; χ^2_M, chi-square test of model fit; df_M, degrees of freedom for model fit; RMSEA, root mean square error of approximation; CI, confidence interval; CFI, comparative fix index; SRMR, standardized root mean square residual. *COMT*, *Catechol-O-methyltransferase*; *BDNF*, *Brain-derived neurotrophic factor.*

CHAPTER 6: STUDY 3

In non-demented aging, executive function performance and change is predicted by *Apolipoprotein E*, intensified by *Catechol-O-methyltransferase* and *Brain-derived neurotrophic factor*, and moderated by age and lifestyle

Introduction

Genetic associations with neurocognitive phenotypes may be magnified as brain resources decline with aging (Belsky et al., 2009; Lindenberger et al., 2008). Single candidate gene association studies have produced encouraging but inconsistent associations with neurocognitive phenotypes in non-demented aging (Harris & Deary, 2011; Laukka et al., 2013; Sapkota, Vergote, Westaway, Jhamandas, & Dixon, 2015). Such single gene-related individual differences in cognitive ability appear to be present, if not increase, in aging (Das et al., 2014; Deary, Penke, & Johnson, 2010). Therefore, recent research has been designed to identify neurobiological mechanisms that may be associated with both maintenance (Nyberg, Lövden, Riklund, Lindenberger, & Bäckman, 2012) and decline (Raz, Rodrigue, Kennedy, & Land, 2009) in a variety of cognitive phenotypes relevant to aging (Harris & Deary, 2011; Raz & Lustig, 2014). This effort has led researchers to pursue even more complex designs, such as those examining (a) interactions among concordant genetic variants and even non-genetic biological and environmental risk factors as they predict (b) longitudinal variations in cognitive performance trajectories (Thambisetty et al., 2013; Thibeau, McFall, Wiebe, Anstey, & Dixon, 2016).

In genetic studies of neurocognitive aging, the most commonly considered polymorphism is *Apolipoprotein E* (*APOE*; rs7412; rs429358). The *APOE* ε4 has been consistently linked to normal cognitive decline (Caselli et al., 2001; Laukka et al., 2013; Luciano et al., 2009; Wisdom, Callahan, & Hawkins, 2011), mild cognitive impairment (Brainerd, Reyna, Petersen, Smith, & Taub, 2011; Dixon et al., 2014), and dementia (i.e., Alzheimer's disease [AD]) (Barral et al., 2012). Although always a promising variant for predicting aging-related cognitive decline, the effects of *APOE* may be moderated by other variants for select cognitive domains. In the present

study, we examine a domain representing everyday goal-oriented performance, namely, executive function (EF). Recent EF research in non-demented aging has concentrated on two commonly studied dopaminergic and neurotrophic related genetic variants (Das et al., 2014; Harris et al., 2006; Nagel et al., 2008; Sapkota et al., 2015) that may interact through basal ganglia-thalamocortical loops (Alexander, DeLong, & Strick, 1986). The single nucleotide polymorphisms (SNPs) identified for dopaminergic and neurotrophic-related factors include *Catechol-O-methyltransferase* (*COMT*; rs4680) (Papenberg et al., 2014; G. Papenberg et al., 2015; Wishart et al., 2011) and *Brain-derived neurotrophic factor* (*BDNF*; rs6265), respectively (Ghisletta et al., 2014; Nagel et al., 2008). In an earlier cross-sectional study, we examined these three polymorphisms and their associations with EF (Sapkota et al., 2015). We observed provisional evidence for synergistic associations. In the present study, we include new longitudinal data to test specific potential dynamic synergies that shed light on the phenomenon and mechanisms associated with EF change in aging (de Frias, Dixon, & Strauss, 2009; Luszcz, 2011). Specifically, we examine independent, additive, and effect modifications of *APOE*, *COMT*, and *BDNF*. Moreover, we adapt contemporary theoretical perspectives that merge neuro-epidemiological and neurobiological evidence to guide our research. According to the brain resource modulation hypothesis (Lindenberger et al., 2008), genetic effects may be magnified in later old age, as compared with younger old adults. Therefore, we examine our dynamic synergistic analyses both for the overall sample and as stratified by age group. Furthermore, some research has shown that lifestyle engagement (especially, physical, cognitive, and social activities) can be related to mechanisms that affect EF performance (Erickson, et al., 2008). For this reason, we test the moderating effects of lifestyle activities on the synergistic associations of

specific genetic variants and potential magnification by chronological age on longitudinal trajectories of EF performance in a 40-year band of non-demented aging.

Our approach to predicting EF performance and change includes systematically examining independent and additive associations for *APOE*, *COMT*, and *BDNF* genetic risk as moderated by age and lifestyle risk factors. The additive (gene + gene) model tests panels of risk, whereby an additional allelic risk may amplify the vulnerability already present with one risk allele (Sapkota et al., 2015; Verhaaren et al., 2013). *APOE* ε4+ allele is present in 40% of dementia cases (Liu, Kanekiyo, Xu, & Bu, 2013), and we may observe an indirect effect of *APOE* ε4+ allele vulnerability in non-demented samples of older adults. Thus, we also examine *APOE* risk status to test effect modification for *COMT* and *BDNF* synergistic associations. The four main steps of approach are as follows. First, we examine independent effects of *COMT*, *BDNF*, and *APOE* and as moderated by age group and a lifestyle activities factor. Second, we test *APOE* moderation for *COMT* and *BDNF* on EF performance and 9-year change. Third, we test whether a set of additive effects (i.e., *COMT* + *BDNF*, *COMT* + *APOE*, *BDNF* + *APOE*) separately and as moderated by age group and lifestyle activities changes EF performance and decline in non-demented aging. Fourth, we test whether an additive effect for *COMT* + *BDNF* is modified by *APOE*. We now summarize the three SNPs as related to cognitive changes in non-demented aging.

APOE is the most commonly studied genetic risk factor for AD and Mild Cognitive Impairment (MCI) (Brainerd et al., 2011; Dixon et al., 2014; Verghese, Castellano, & Holtzman, 2011). It is differentiated by three isoforms: ε2, ε3, and ε4. Carriers of the ε4 allele have been associated with a higher risk of AD development (Wisdom et al., 2011). In contrast, the ε2 allele has been found to be potentially protective in numerous studies (Corder et al., 1994; de-Almada

et al., 2012; McFall et al., 2015; Panza et al., 2000). The *APOE* gene has been reported to have an antagonistic pleiotropy effect, whereby the gene may be beneficial at a younger age but harmful with increasing age (Jochemsen, Muller, van der Graaf, & Geerlings, 2012). Thus, most studies focus on older adult groups to investigate *APOE*-cognition associations both concurrently and varying longitudinal periods. *APOE* is involved in transporting cholesterol to neurons, which is crucial for synaptic formation and axonal growth important in learning, memory, and injury repair. In addition, the *APOE* genotype presents an allelic dosage effect whereby the ε4/ε4 allele is associated with the highest risk followed by ε3/ε3 and ε2/ε2 (Liu et al., 2013). *APOE* ε4 allelic risk is related to dendritic spine density in the hippocampus and neuroinflammation (Fotuhi, Hachinski, & Whitehouse, 2009; Liu et al., 2013), but not all evidence is supportive (Bunce et al., 2012). Current reports focus on synergistic associations of *APOE* in normal aging with other biological (i.e., genetic polymorphisms; (Das et al., 2014; Sapkota et al., 2015)) and vascular-health (i.e., pulse pressure; (McFall et al., 2015)) risk factors.

The *COMT* (rs4680) Val158Met polymorphism increases COMT enzyme activity that in turn decreases dopamine (DA) levels primarily in the prefrontal cortex (Bilder, Volavka, Lachman, & Grace, 2004; Chen et al., 2004; Papenberg et al., 2014). The prefrontal cortex has significantly greater numbers of dopaminergic pathways (Raz et al., 2009), which have been associated with EF processes (Bäckman, Lindenberger, Li, & Nyberg, 2010). The *COMT* polymorphism at codon 158 on chromosome 22q11 results in the *COMT* homozygotes for the Met allele having greater DA levels compared to the Val allele homozygotes. Thus *COMT* Met homozygotes have higher levels and longer period of DA levels at synapses, which excites prefrontal neurons and allows for better information processing (Das et al., 2014; Egan et al., 2003). Carriers of the Val allele may be at higher risk for brain and cognitive deficits, including

executive functioning (Das et al., 2014; Nagel et al., 2008; Sapkota et al., 2015; Wishart et al., 2011) and reduced white matter integrity (Papenberg et al., 2015).

The *BDNF* (rs6265) Val66Met polymorphism located at 11p13 (Houlihan et al., 2009) is involved in decreased BDNF secretion and may be associated with normal cognitive decline (Egan et al., 2003) and impairment leading to AD-related dementia (Komulainen et al., 2008; Raz et al., 2009). BDNF is mostly present in hippocampus and prefrontal cortex, and plays an important role in memory, EF (Nagel et al., 2008; Sapkota et al., 2015), and cognitive plasticity (Poo, 2001). The *BDNF* Met allele is considered to be the risk allele as it leads to lower levels of BDNF in the hippocampus and pre-frontal cortex. *BDNF*-cognition association studies have reported an inconsistent pattern of results. For example, a recent meta-analysis examined 23 publications with a combined total of 7095 individuals and did not observe significant associations with all of the five most commonly studied phenotypes: general cognition, memory, EF, visual processing, and verbal fluency (Mandelman & Grigorenko, 2012).

Our research approach reflects a magnification perspective whereby more than one copy of a risk allele, even across genotypes, may intensify the deleterious effects of genetic risk, especially in older and/or less active adults. We examine independent and additive synergistic associations to investigate the underlying mechanisms associated with genetic risk and aging over a 9-year period of EF change, covering a 40-year band of aging. As noted, the present study is a major extension of an earlier and promising cross-sectional study which focused on determining the optimal operations for combining these variants (additive or multiplicative) in terms of examining synergistic effects of *COMT* and *BDNF* on EF in non-demented older adults (Sapkota et al., 2015). The present study adopts the additive operation combined with tests of moderation by *APOE* and potential magnification by chronological age and lifestyle activities. In

addition, using a procedure established earlier (McFall et al., 2014), we measure EF as a single latent variable indicated by four standardized neuropsychological manifest tests. Finally, as is necessary in longitudinal work, we also tested and established longitudinal invariance of the EF factor.

Research Questions

We examined two general research questions, each containing two parts. In research question 1, we tested independent associations of *COMT*, *BDNF*, and *APOE*. In research question 2, we tested additive associations of *COMT* + *BDNF*, *COMT* + *APOE*, *BDNF* + *APOE* on EF performance and 9-year change as separated by age groups and lifestyle activity level. Both research questions were divided into two parts. In parts 1a and 2a we examined all three genotypes. In part 1b, we tested *APOE* moderation effect of *COMT* and *BDNF* (research question 1b) as separated by age group and lifestyle activity level. In part 2b, we tested *APOE* effect modification for *COMT* + *BDNF* (research question 2b) as separated by age group and lifestyle activity level. Based on our previous cross-sectional study, we expected to observe *APOE* moderation and effect modification for *COMT* and *BDNF* genotypes on EF performance and change.

Research question 1a (RQ1a): Do allelic risk carriers for *COMT* (Val/Val; Val/Met), *BDNF* (Met/Met; Met/Val), and *APOE* (ε4+) show poorer performance and steeper decline in EF than their non-risk counterparts? We test this question independently, by age group (<70 years old versus ≥ 70 years old), and by lifestyle activities (high versus low activities)? We expected allelic risk carriers to have poorer EF performance and steeper decline overall. We also expected worse performance and decline in the older group or the low lifestyle activities group than in the younger or the high lifestyle activities groups.

Research question 1b (RQ1b): Does *APOE* status (ε4+ versus ε4-) moderate EF performance for *COMT* and *BDNF* allelic risk carriers such that *COMT* and *BDNF* allelic risk carriers in the *APOE* ε4+ group have poorer EF performance and steeper decline than those in the *APOE* ε4- group? Second, we examined whether this effect was exacerbated in the older or low lifestyle activities groups compared to the younger or high lifestyle activities group.

Research question 2a (RQ2a): Does the additive (gene + gene) risk effect for each combination (i.e., *COMT* + *BDNF*, *COMT* + *APOE*, *BDNF* + *APOE*) exacerbate EF performance or decline? Is this exacerbation overall, by age group (younger versus older), or by lifestyle activities (high versus low activities)? We expected that the cumulative effect of higher allelic risk would produce poorer EF performance and steeper decline than would the non-risk combinations, especially in the older age and low lifestyle activities group.

Research question 2b (RQ2b): Do *APOE* ε4+ carriers have poorer EF performance and steeper decline with increasing allelic risk in the *COMT* + *BDNF* risk panel compared to the *APOE* ε4- group. Is this expected effect more deleterious in the older group than the younger group or in the low lifestyle activities group than in the high lifestyle activities group? We expected *APOE* ε4+ carriers in the older group and in the low lifestyle activities group to have poorer EF performance and steeper decline with increasing risk in the *COMT* + *BDNF* risk panel compared to older adults in *APOE* ε4- group.

Method

Participants

This study uses data from the Victoria Longitudinal Study (VLS), a large scale, longitudinal sequential study examining biomedical, health, genetic, and neurocognitive aspects of aging. General information on recruitment, methodological, and VLS characteristics are

available elsewhere (Dixon & de Frias, 2004; Dolcos, MacDonald, Braslavsky, Camicioli, & Dixon, 2012). All volunteers in the VLS were initially healthy, enrolled through advertisements, and received a small honorarium for their participation. The VLS and all present data collection procedures are in full and certified compliance with prevailing human/institutional research ethics guidelines. Written informed consent was obtained from all participants. All participants were Caucasian with complete access to Canadian national health care. The present sample reflects the implementation of exclusionary criteria affecting individuals with (a) diagnosis or history of dementia, (b) anti-psychotic medication, (c) Mini Mental State Exam (MMSE) scores less than 24, (d) uncontrolled hypertension, (e) insulin-controlled diabetes, and (f) history of serious head injury (e.g., hospitalized). Accordingly, n = 634 participants (age range = 53-95 years, mean age = 70.58, SD = 8.65) including 423 females and 211 males with genetic data were included at baseline (see Table 6-1; Table 6-2). We followed an accelerated longitudinal design by assembling three samples from the VLS. The present Wave 1 (W1) and Wave 2 (W2) included participants from all three samples and Wave 3 (W3) included participants from Sample 3. We had (a) Sample 1 (S1) Waves 6 and 7, (b) Sample 2 (S2) Waves 4 and 5, and (c) Sample 3 (S3) Waves 1, 2, and 3. Throughout this report, (a) W1 (n = 634) refers to S1W6, S2W4, and S3W1, (b) W2 (n = 518) refers to S1W7, S2W5, S3W2, and (c) for W3 (n = 294) refers to S3W3 (see Table 6-1). We note that age and MMSE scores for *BDNF* genotype were significantly different between the three allelic risk groups at W2 (Table 6-1). The average interval between each waves were 4.4 years between W1 and W2, and 4.5 years between W2 and W3. W1 and W2 included participants from S1-S3 and W3 had participants from only S3. The retention rate for each wave interval for (a) S1: W1-W2 is 83%, (b) S2: W1-W2 is 77%, (c) S3: W1-W2 is 84%, (d) S3 W2-W3 is 88%, and (e) S3 W1-W3 is 74% .

DNA Extraction and Genotyping

Saliva was collected according to standard procedures from Oragene DNA Genotek and stored at room temperature in Oragene® disks until DNA extraction. DNA was manually extracted from 0.8 ml of saliva sample mix using the manufacturer's protocol with adjusted reagent volumes. Genotyping was carried out by using a PCR-RFLP strategy to analyze the allele status for *BDNF* (rs6265), *COMT* (rs4680), and *APOE* (rs7412, rs429358). Genotyping was successful for the targeted SNPs for all present participants. Table 6-1 shows participant characteristics by genotype for *BDNF*, *COMT,* and *APOE*. The genotype frequencies for the three examined genotypes did not differ significantly from Hardy-Weinberg equilibrium at baseline: *BDNF* rs6265 ($\chi^2 = 0.837$, $p = 0.36$), *COMT* rs4680 ($\chi^2 = 2.786$, $p = 0.10$), and *APOE* rs7412, rs429358 ($\chi^2 = 0.545$, $p = 0.909$). For purposes of analyses we included all three allelic combinations for *COMT* and *BDNF* (Met/Met, Met/Val, and Val/Val). Both SNPs were coded from 1 to 3 (3 = highest risk). For evaluating moderation and effect modification by *APOE*, we deleted all ε2/ε4 carriers ($n = 30$) and then compared patterns between ε4+ carriers and ε4- group. *APOE* ε4- group was coded as 1 (no risk) and *APOE* ε4+ group as 2 (risk).

Executive Function Measures

Two dimensions of EF (inhibition, shifting) were each measured by two standard and frequently used tests for both behavioral and clinical studies in older adults (de Frias et al., 2006; McFall et al., 2014; McFall et al., 2013; Sapkota et al., 2015).

Hayling Sentence Completion (Hayling; Inhibition). This test (Burgess & Shallice, 1997) consists of two sections, each comprising 15 sentences. In the first section, participants must state the last word that correctly completes the sentence. In the second section, the participants must say a word that is not at all related to the sentence. The standardized scores are

based on an error score from the second section and the speed of each response from both sections, which are then combined to obtain the final score (1 = impaired to 10 = superior).

Stroop (Inhibition). This test (Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997) consists of three parts. In part A, participants are asked to name four different colors that appear as 24 dots in six different rows. In part B, the same colors appear but are printed as common words. In part C, each different color is represented as a textual representation, with the text being the name of its corresponding color. The participants are measured based on latencies. The final score is the standardized Stroop interference index ([Part C- Part A]/ Part A), with a lower index reflecting better performance.

Brixton Spatial Anticipation (Brixton; Shifting). This test (Burgess & Shallice, 1997) consists of 10 different circles; one being blue while the rest are colorless. The circles appear in a 56-page booklet. The blue colored circle shifts position with some logical pattern after each page. This test measures the mechanism of shifting by asking participants to guess where the blue colored circle will appear on the next page. The total number of incorrect guesses are measured and the final scores are calculated (1 = impaired to 10 = superior).

Color Trails (Shifting). This test (D'Elia, Satz, Uchiyama, & White, 1996) comprises of two different tasks in which participants connect different attributes, such as numbered and colored circles. In the first section, participants connect numbers from 1–25 within circles that are randomly organized on a page. In the second section, they connect the numbers in order but alternating between pink and yellow circles. Latency scores in the second section were computed and used in the final analyses. Lower scores reflected better performance.

Lifestyle activities composite

The VLS Activity Lifestyle Questionnaire (VLS-ALQ) with 67-items was used to determine the level of activity for the following four domains: (a) social, such as visiting friends (7 items); (b) physical activity, such as gardening (4 items); (c) integrative information processing, such playing a musical instrument (12 items); and (d) novel information processing, such as completing jigsaw puzzles (27 items). The frequency of participation is rated on a 9-point scale (never, less than once a year to two or three times a week, and daily). All the items within each domain were summed, with higher scores representing greater frequency of activity (Hultsch, Hertzog, Small, & Dixon, 1999; Small, Dixon, McArdle, & Grimm, 2012). Lifestyle activities composite was calculated by summing the scores across all four domains.

Statistical Analysis

Structural equation modeling (SEM) was used to analyze both parts of the two research questions with Mplus Version 7 (Muthén & Muthén, 1998-2015). All missing values for cognitive measures were assumed to be missing at random and handled using maximum likelihood. Missing predictor values were handled using list-wise deletion in Mplus. Only two participants with missing measures on all four EF tasks were lost due to list-wise deletion.

Preliminary factor analyses for EF latent variable. In the first preliminary analysis, we tested and confirmed a previously established one-factor EF latent variable (Sapkota et al., 2015). Specifically, CFA was used to examine loadings of all four manifest variables (Stroop, Hayling, Brixton, and Color trails) on the predicted latent variable. The first model tested all observed variables on one latent EF factor and the second model tested a two-factor shifting and inhibition model. The best fitting model was determined by examining several fit statistics. The chi-square test of model (χ^2; $p > .05$) allowed for an overall indication of good model fit. Additional absolute/comparative fit indices were also examined to determine a good model fit to

the data (Kline, 2011). These included the root mean square error of approximation (RMSEA ≤ .05), comparative fix index (CFI ≥ .95), and the standardized root mean square residual (SRMR ≤ .08).

In the second preliminary analysis, we established longitudinal invariance across all three waves for the best factor. We started with configural invariance, which establishes that all four indicators load on to the same factor. Second, metric invariance tests whether the unstandardized factor loadings at Waves 1-3 can be constrained and set to be equal to each other. Third, scalar invariance examines whether the four EF indicator intercepts can be constrained to be equal across all waves. Fourth, equal residuals invariance examines whether the EF factor can explain the same amount of variability across the three waves. We obtained partial scalar longitudinal invariance across all three waves (see Table 6-3). Age was centered at 75 years and EF factor scores were computed to test both research questions.

In the third preliminary analysis, we determined the best latent growth model for our one factor EF latent variable. We adopted a model building approach and started with a simple (null) model, and added parameters at each step to arrive at a baseline model of change. The null model assumes that there is no change over five waves, followed by the addition of fixed intercepts, random intercepts, fixed slope, random slope, and fixed quadratic. First, in the null model, the variances for the intercepts were fixed across adults to 0. Second, in the random intercepts model, individuals were allowed to vary in intercept variance by removing the fixed intercept at 0. Third, a fixed linear slope was added to the baseline model by fixing the slope to 0 across all adults. The fixed linear slope assumed that all participants were changing in performance at the same rate. Fourth, adults were allowed to vary in their slope performance by removing the fixed linear slope constraint, and adding a random intercept and random linear slope model of change.

Fifth, a fixed quadratic was added to the random intercept and random linear slope model, where both the intercepts and the slope were allowed to vary across individuals, but the curvilinear change was fixed across all participants. Following the examination of model fit, the χ^2difference statistic was calculated to detect any improvement in fit with the addition of free parameters at each step. The random intercept and random slope model was the best fit for our one-factor EF latent variable (see Table 4) and was used in all subsequent analyses.

Analyses for research questions. Older adults who were age 70 years and older were in the old-old (OO) group and those below 70 years were in the young-old (YO) group. In the YO group, age was centered at 63 years and in the OO group, age was centered at 77 years, based on the mean age in each group. The lifestyle activities composite was split into low and high activities at the overall mean lifestyle activities score of 133. Older adults below 133 were in the low activities group and adults with at least a score of 133 or above were in the high lifestyle activities group. Although we used the three waves to organize the demographic information (Table 6-1), it is important to note that wave was not used as the metric of longitudinal change in the analyses. Specifically, age was used as the metric of change. Statistically, using age in this manner permits us to account for variability associated with age as well or better than if it is used as a covariate in the statistical models. Gender and education (continuous) were used as covariate in all analyses. For model fit statistics and significant results, we examined the regression estimate and $p < .05$, and -2 log likelihood (-2LL), Akaike information criteria (AIC), and Bayesian information criteria (BIC) values with lower values indicating better model fit (see Table 5). We now turn to analyses for each research question.

For RQ1a, EF was regressed on *APOE*, *COMT*, and *BDNF* independently, and as separated by age group (YO and OO) and lifestyle activities composite (low and high activities).

For RQ1b, EF was regressed on *COMT* and *BDNF* as separated by *APOE* status (ε4+ versus ε4-). Next, we tested this regression model as further separated by age group (YO and OO) and lifestyle activities composite (low and high).

For RQ2a, EF was regressed separately on all additive genetic combinations. Specifically, for the additive models we tested (a) *COMT* + *BDNF*; (b) *COMT* + *APOE*; and (c) *BDNF* + *APOE*. We tested all three models independently, and as separated by age group (YO and OO) and lifestyle activities composite (low and high activities).

For RQ2b, EF was regressed on *COMT* + *BDNF* additive model as separated by *APOE* status (ε4+ versus ε4-). Next, we tested this regression model as further separated by age group (YO and OO) and lifestyle activities composite (low and high).

Results

In our preliminary analyses, we established that the one-factor parsimonious model of EF provided the best fit to the data and was used as the final CFA model. Unstandardized regression coefficients for the expected EF latent variable were examined to determine differences and change in performance. For longitudinal invariance, we obtained partial scalar longitudinal invariance across all three waves ($\chi^2(df)$ = 84.60 (49), p = .001; *RMSEA* (90% CI) = .034 (.021-.044); *CFI* = .977; and *SRMR* = .084) (Table 6-3). Next, we computed EF factor scores, which were used in all succeeding models for RQ1 and RQ2. The best latent growth model was obtained with the random intercept and random slope model (Table 6-4).

For RQ1a, we observed four significant independent effects of *APOE* on EF performance and change. First, overall, *APOE* risk carriers (ε4+) performed worse than their non-risk (ε4-) counterparts at age 75 (β = -0.206; SE = 0.098; p = .036) (Table 6-5; Figure 6-1a). We did not observe significant differential decline between the *APOE* ε4+ and ε4- group. Second, in the YO

group, *APOE* ε4+ carriers performed worse on EF than their ε4- counterparts at age 63 (β = -0.210; SE = 0.100; p = .036) and had steeper decline over the 9-year period (β = -0.015; SE = 0.007; p = .020). Third, in the OO group, *APOE* ε4+ carriers had steeper decline on EF with age than their non-risk (ε4-) counterparts (β = -0.029; SE = 0.011; p = .007) (Figure 6-2). Levels of lifestyle activities did not significantly moderate *APOE* genotype on EF performance or change. We did not observe significant independent effects for *COMT* or *BDNF* allelic risk on EF performance or change independently (Figure 6-1b and 6-1c), or as separated by age (Figure 6-3 and 6-4) or lifestyle activities group.

For RQ1b, we observed three significant associations. First, in the overall group, there was a significant moderation effect for *BDNF* genotype by *APOE* status (ε4- versus ε4+). Specially, *BDNF* Met/Met homozygotes in the *APOE* ε4+ group had the worst EF performance at age 75 years compared to the *BDNF* Val/Met or Val/Val genotype (β = -0.373; SE = 0.179; p = .037). *BDNF* allelic risk carriers in the *APOE* ε4- group performed relatively well, as compared with that of the *APOE* ε4+ group (Figure 6-5). Regarding *COMT*, *APOE* status effects are consistent with an inference of protection (Figure 6-6). Second, in the YO group, *BDNF* Met/Met homozygotes in the *APOE* ε4+ group had the worst EF performance at age 63 years (β = -0.330; SE = 0.145; p = .023) and slower increase on EF (β = -0.032; SE = 0.010; p = .023) than the *BDNF* no-risk (Val/Val) homozygotes (Figure 6-7). Third, in the high lifestyle activities group, *BDNF* Met/Met homozygotes in the *APOE* ε4+ group had the worst EF performance at 75 years (β = -0.525; SE = 0.252; p = .037) (Figure 6-8), but no significant difference on EF change.

For RQ2a, we did not observe any significant effects for (a) *COMT* + *BDNF*, (b) *COMT* + *APOE*, or (c) *BDNF* + *APOE* risk independently, as separated by age (YO and OO) or lifestyle activities (low and high) group.

For RQ2b, we observed two significant synergistic effects for the *COMT* + *BDNF* combination. First, *APOE* effect modification was observed for *COMT* + *BDNF* additive effect on EF performance. *COMT* + *BDNF* allelic risk showed an additive risk effect at age 75 and borderline decline in the *APOE* risk (ε4+) group. Specifically, older adults displayed poorer EF performance with increasing allelic risk in the *COMT* + *BDNF* risk panel at age 75 (β = -0.307; SE = 0.123; p = .013), and borderline 9-year decline (β = -0.012; SE = 0.006; p = .054) (Table 6-5; Figure 6-9). Second, an increase in *COMT* + *BDNF* allelic risk was associated with a less steeper decline in EF performance for *APOE* ε4- group with high lifestyle activities (β = 0.008; SE = 0.004; p = .046) (Figure 6-10). We did not observe any significant effects for *COMT* and *BDNF* cumulative risk as divided by *APOE* ε4 status and age group.

Discussion

We tested independent and additive associations of *APOE*, *COMT*, and *BDNF* allelic risk as separated by age and lifestyle risk on EF performance and 9-year change in non-demented older adults. In addition, we also tested (a) *APOE* moderation effect for *COMT* and *BDNF* and (b) *APOE* effect modification for additive associations of *COMT* + *BDNF*, and as separated by age (YO versus OO) and lifestyle activities (high versus low) groups. Some recent research has begun to examine independent, interactive, and additive associations for these three genetic variants and cognitive performance in older adults (McFall et al., 2015; Nagel et al., 2008; Papenberg et al., 2014; Sapkota et al., 2015; Wishart et al., 2011). To our knowledge this is the first study to examine independent and additive associations with EF performance and change as separated by age group and lifestyle activities for these three variants in a longitudinal sample of non-demented older adults. Key results include the following. First, we observed that *APOE* ε4+ carriers were at higher risk for poor EF performance and steeper decline overall. Second, *APOE*

ε4+ carriers moderated *BDNF* genotype in that *BDNF* allelic risk carriers were at an increased risk especially in the younger age and high lifestyle activities group. Third, *APOE* ε4+ carriers magnified the *COMT* + *BDNF* panel effect on EF but this effect was not present in the high lifestyle activities group. We now discuss each of our main findings.

First, we observed independent effects of *APOE* on EF performance overall and as separated by age group. As expected, *APOE* risk carriers (ε4+) performed worse than their non-risk (ε4-) counterparts at age 75 years in the overall group, at age 63 years in the YO group, and had steeper EF decline in the OO group. Although some previous research and meta-analyses on *APOE* and cognitive associations have reported similar findings in non-demented older adults, observers have also concluded that the associations may be specific to cognitive domain (Marioni et al., 2015; Raz et al., 2009; Small, Rosnick, Fratiglioni, & Bäckman, 2004). We did not observe *COMT* and *BDNF* allelic risk differences in EF predictions, but we found an expected age magnification effect whereby adults in the OO group were declining more in EF performance than their YO counterparts (Figure 6-3 and 6-4). Notably, for low versus high lifestyle activities, we observed a similar pattern of results. Specifically, there were no independent effects of *APOE*, *COMT*, and *BDNF* in the two groups but adults with high lifestyle activities showed less decline in EF performance compared to those with low lifestyle activities.

Second, we observed an *APOE* moderation effect for *BDNF* genotype on EF performance in the overall group, in the YO group, and in the group with high lifestyle activities. *BDNF* Met/Met homozygotes showed the worst EF performance only in the presence of *APOE* ε4+ allelic risk, and this effect was magnified when examined with potential protective factors, such as younger age and higher lifestyle activities. A similar *APOE* and *BDNF* interactive effect was reported for episodic memory performance (Ward et al., 2014). This study found that *BDNF*

Met+ carriers with *APOE* ε4 allele had poorer performance compared to *BDNF* Met+ carriers with the *APOE* ε2 allele. They hypothesized a potential biological interaction between *BDNF* and *APOE* encoded proteins may influence cognitive function. Another recent study examined amyloid beta deposition in cognitively normal older adults (Adamczuk et al., 2013) suggesting a possible biological mechanism between *APOE* ε4 status and *BDNF* Met carriers. Specifically, *APOE* ε4+ carriers with *BDNF* Met+ genotype had higher amyloid load than *BDNF* Met- genotype in the precuneus, orbitofrontal cortex, gyrus rectus, and lateral prefrontal cortex. They suggest that the lipid metabolism pathway influenced with the *APOE* genotype and the role of *BDNF* on neuronal survival may be linked in way that results in lower or higher amyloid-deposition. In the present study, *BDNF* Met carriers are only at disadvantage if *APOE* ε4 risk is moderating the association on EF performance. We also observed that this moderation effect was magnified in YO adults and in those with higher lifestyle activities. YO adults are shown to be more physically active than OO adults (Evenson, Buchner, & Morland, 2012) and those with high lifestyle activities are highly engaged in physical, social, and cognitive processing activities than their low lifestyle activities counterparts (Runge, Small, McFall, & Dixon, 2014). Physical activity has been shown to increase BDNF expression in the brain, and this can result in both greater synaptic plasticity (Cotman & Berchtold, 2002) and reduced memory impairment (Erickson, Miller, & Roecklein, 2012). The *BDNF* gene controls BDNF levels. *BDNF* Met carriers have a lower expression of BDNF (Mata, Thompson, & Gotlib, 2010), which has been associated with poor cognitive functioning (Savitz, Solms, & Ramesar, 2006). However, increasing BDNF levels through activities (i.e., exercise) may mediate memory impairment in *BDNF* Met carriers (Erickson et al., 2012). Thus, *BDNF* genotype differences for *APOE* ε4+ carriers in the YO group and with high lifestyle activities may be selectively magnified through

increased BDNF expression for those at high genetic risk for cognitive impairment. We also observed an age and lifestyle activities effect where older age and low lifestyle activities resulted in EF decline despite *BDNF* and *COMT* allelic risk differences for both *APOE* ε4+ carriers and non-carriers. The *APOE* moderation effect on *BDNF* in our study implies that the (a) *BDNF* Met/Met risk may only be detrimental for EF performance in the presence of *APOE* ε4+ risk, and (b) younger age and high lifestyle activities may mitigate some of the risk associated with *BDNF* Met/Met homozygotes perhaps by increasing BDNF expression.

Third, we observed an *APOE* effect modification for *COMT* + *BDNF* additive association on EF performance. *APOE* ε4+ carriers displayed poorer EF performance with increasing allelic risk in the *COMT* + *BDNF* risk panel at age 75 and borderline 9-year decline. An additional allelic risk for either *COMT* or *BDNF* gene in *APOE* ε4+ carriers resulted in poorer EF performance whereas, *APOE* non-risk carriers (ε4-) were protected from the deleterious effect of *COMT* + *BDNF* allelic risk. Previous studies have reported lower prefrontal DA levels and poor cognitive processing in *COMT* Val/Val homozygotes (Papenberg et al., 2014), with age altering this relationship (Bäckman et al., 2010; Lindenberger et al., 2008). Although we did not observe differential patterns in our YO versus OO age groups, we informally note a borderline aging magnification of *COMT* + *BDNF* genetic effects across a 40-year continuum from 55 to 95 years. Recent studies have reported the aging related magnification of genetic effects (Papenberg, Lindenberger, & Bäckman, 2015) for *COMT*. An inverted U-shaped curve has been proposed to describe this relationship, whereby *COMT* Met/Met homozygotes with higher DA levels are associated with better cognitive performance. However, this association deteriorates as brain resources begin to decline with aging (Lindenberger et al., 2008). As for *BDNF* Val/Val homozygotes, they have higher levels of neurotrophic factors (Marosi & Mattson, 2014), which

has been associated with better cognitive performance (Nagel et al., 2008). In our additive association, we observed that an absence of *COMT* Val+ or *BDNF* Met + allelic risk does not eliminate the risk present with either *COMT* or *BDNF* genotype for *APOE* ε4+ carriers on EF performance. As expected, older *APOE* ε4+ carriers with the highest cumulative genetic risk for *COMT* (Val/Val homozygotes) in addition to *BDNF* (Met/Met homozygotes) had the worst EF performance. However, this *APOE* effect modification was not present in *APOE* ε4+ carriers with high lifestyle activities. Some past studies show that varying life experiences including high leisure and mental activities may be protective against dementia onset (Scarmeas, Levy, Tang, Manly, & Stern, 2001; Valenzuela, Brayne, Sachdev, & Wilcock, 2011) or supporting non-demented cognitive maintenance (Erickson et al., 2008; Thibeau et al., 2016). The proposed mechanisms are activity-or exercise-related increases in synaptic density and cognitive reserve, which may delay clinical symptoms (Scarmeas et al., 2001) and promote maintenance of brain reserve in old age (Wang, Karp, Winblad, & Fratiglioni, 2002). Thus, high lifestyle activities may counteract the negative effects and be most beneficial to adults with the highest combination of genetic risk (i.e., *COMT* + *BDNF* allelic risk for *APOE* ε4+ carriers than non-carriers). We also observed that the very high-risk group for *COMT* + *BDNF* in the *APOE* ε4- group showed the least decline in EF performance over 9 years (Figure 9). Our results support the "differential susceptibility" model (Belsky et al., 2009; Ferencz et al., 2014), which suggests that adults with the highest allelic risk show the greatest amount of plasticity.

Although the risk associated with one variant was still present, we expected to observe that a protective allele in the overall group, and especially in the YO age group or high lifestyle activities group, would reduce the risk associated with other SNP (Harris et al., 2014; Purcell et al., 2009; Sapkota et al., 2015; Verhaaren et al., 2013). Such a process could result in

significantly less detrimental effects on EF performance and change. Accordingly, this supports one main finding of the present study. The *APOE* genotype does not appear to play a cumulative role with *COMT* and *BDNF* but rather moderates *BDNF* genotype and presents an effect modification of the *COMT* + *BDNF* additive effects on EF performance and change. Furthermore, this association is magnified through differences in chronological age group and supportive lifestyle activity levels. Thus, we propose that the potential biological mechanism is associated with *APOE* ε4 positivity and is selectively intensified through *COMT* and *BDNF* allelic risk, as further determined by age and level of lifestyle activities.

We now note several strengths and limitations of the present study. For our strengths, first, we included a large sample of older adults (n = 634) tested across a 40-year band of aging (age range = 53-95 years) from the VLS project. The design allowed us to examine age magnification over 40 years and test difference between two age groups (YO and OO) split at 70 years old. Second, we used an accelerated longitudinal design with age as the metric of change thereby incorporating chronological age into our analyses. This advanced latent growth modeling technique accounts for any missing waves for participants and maximizes the use of our longitudinal data to accurately test our research goals. Third, we used four standard neuropsychological tests contributing to a one-factor EF latent variable. Previous studies usually only report the use of single manifest variables (e.g., Color trails) to examine candidate gene associations. Thus, our EF latent variable takes into account any errors associated single cognitive tests. For our limitations, first, we examined only one neuropsychological domain, EF. Future studies should consider examining other domains including neurocognitive speed and memory with *APOE*, *COMT*, and *BDNF*. Second, lifestyle activities were based on frequency and we did not take into account the extent of participation in all the physical, social, integrative

and novel information processing activities. The VLS Activities Lifestyle Questionnaire has been previously validated (e.g., Hultsch et al., 1999). We note that some related objective measures were available for the domain of physical activities (i.e., timed-walk speed, hand grip strength) and future studies may consider using both objective and self-reported measures. Third, because of ongoing data collection schedules, the longitudinal design did not include a third-wave opportunity for all participants. However, our results seem not to have been compromised. Moreover, our analyses use all data points available for all participants. In addition, we tested and confirmed that the EF latent variable performed with measurement invariance across all waves.

In conclusion, in aging the *APOE* genotype presents an (a) overall independent effect, (b) moderation effect on *BDNF* genotype, and (c) effect modification of *COMT* + *BDNF* additive associations on EF. In addition, both chronological age and lifestyle activities may moderate these associations. It is important to note that high lifestyle activities may potentially protect against expected cognitive decline associated with cumulative genetic risk (*COMT* + *BDNF*). Influential and interacting mechanisms of aging and genetic magnification effects on EF in non-demented older adults may be detected only in the presence of *APOE* ε4+ carriers and enhanced through the protective lens of lifestyle activities. Such results may clarify the often-noted inconsistencies in single-gene *COMT* and *BDNF* association studies and point toward the importance of multi-factorial approaches to understanding neurobiological aging and influences on cognitive aging.

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Table 6-1

Participant characteristics by wave and genotype

Characteristics												
Wave 1		***COMT***				***BDNF***				***APOE***		**Total**
	Met/Met	**Met/Val**	**Val/Val**	***p*-value**	**Met/Met**	**Met/Val**	**Val/Val**	***p*-value**	**ε4-**	**ε4+**	***p*-value**	
n	146	338	150	--	27	189	418	--	455	149	--	634
Age (years)	70.15 (8.86)	70.85 (8.68)	70.40 (8.40)	0.686	68.54 (6.32)	71.45 (8.52)	70.32 (8.81)	0.150	70.91 (8.83)	69.86 (8.27)	0.203	70.58 (8.65)
Education (years)	14.92 (3.11)	15.35 (2.80)	15.36 (3.15)	0.303	15.72 (2.70)	15.13 (2.99)	15.28 (2.96)	0.590	15.19 (2.97)	15.55 (3.07)	0.201	15.25 (2.96)
Gender (F/M)	101/45	226/112	96/54	0.639	18/9	128/61	277/141	0.940	305/150	93/56	0.303	423/211
MMSE	28.72 (1.20)	28.72 (1.20)	28.56 (1.32)	0.403	29.15 (0.77)	28.74 (1.15)	28.62 (1.28)	0.068	28.66 (1.24)	28.68 (1.25)	0.894	28.68 (1.23)
Wave 2		***COMT***				***BDNF***				***APOE***		
	Met/Met	**Met/Val**	**Val/Val**	***p*-value**	**Met/Met**	**Met/Val**	**Val/Val**	***p*-value**	**ε4-**	**ε4+**	***p*-value**	
n	119	276	123	--	25	158	335	--	377	117	--	518
Age (years)	73.91 (8.78)	75.12 (8.65)	74.57 (8.18)	0.429	73.11 (6.66)	76.12 (8.49)	74.17 (8.67)	0.041	75.09 (8.68)	73.66 (8.33)	0.118	74.71 (8.57)
Education (years)	15.24 (3.09)	15.50 (2.72)	15.55 (3.03)	0.648	15.82 (2.79)	15.26 (2.99)	15.51 (2.84)	0.527	15.36 (2.88)	15.89 (3.00)	0.088	15.45 (2.88)
Gender (F/M)	81/38	184/92	78/45	0.728	16/9	106/52	221/114	0.943	251/127	73/44	0.437	
MMSE	28.49 (1.67)	28.47 (1.35)	28.49 (1.31)	0.984	29.16 (0.85)	28.44 (1.49)	28.44 (1.41)	0.047	28.53 (1.31)	28.27 (1.71)	0.079	28.48 (1.42)
Wave 3		***COMT***				***BDNF***				***APOE***		

	Met/Met	**Met/Val**	**Val/Val**	***p*-value**	**Met/Met**	**Met/Val**	**Val/Val**	***p*-value**	**ε4-**	**ε4+**	***p*-value**	
n	64	152	78	--	12	92	190	--	211	67	--	294
Age (years)	75.29 (7.20)	74.38 (7.48)	75.99 (6.93)	0.270	74.21 (6.51)	76.06 (7.24)	74.54 (7.33)	0.242	75.33 (7.40)	73.98 (6.91)	0.189	75.01 (7.28)
Education (years)	15.09 (2.91)	15.77 (2.82)	15.62 (3.22)	0.301	16.38 (3.26)	15.31 (2.84)	15.66 (2.99)	0.422	15.43 (2.92)	16.16 (3.17)	0.084	15.58 (2.96)
Gender (F/M)	44/20	104/48	51/27	0.879	9/3	62/30	128/62	0.859	144/67	43/24	0.538	28.68 (1.41)
MMSE	28.61 (1.84)	28.69 (1.27)	28.76 (1.40)	0.830	28.83 (1.53)	28.56 (1.63)	28.75 (1.26)	0.539	28.64 (1.47)	28.79 (1.18)	0.462	28.69 (1.40)

Note. *n* = total number; *COMT = Catechol-O-methyl transferase*; *BDNF = Brain-derived neurotrophic factor*; *APOE = Apolipoprotein E*; $p < .05$. MMSE = Mini-Mental State Exam. Standard deviations are in parentheses. For the analyses involving the *APOE* genotypes, the ε2/ε4 carriers (*n* = 30) were deleted from the sample.

Table 6-2

Participant characteristics by age group and genotype

Characteristics												
Young-Old		***COMT***				***BDNF***				***APOE***		**Total**
	Met/Met	**Met/Val**	**Val/Val**	***p*-value**	**Met/Met**	**Met/Val**	**Val/Val**	***p*-value**	**ε4-**	**ε4+**	***p*-value**	
n	70	152	74	--	15	79	202	--	201	79	--	296
Age (years)	62.32 (4.47)	62.70 (4.58)	63.37 (4.39)	0.356	64.09 (4.63)	63.10 (4.24)	62.55 (4.60)	0.333	62.50 (4.52)	63.28 (4.44)	0.191	62.77 (4.51)
Education (years)	15.21 (3.01)	15.73 (2.75)	15.38 (3.25)	0.418	15.77 (2.97)	15.15 (3.09)	15.65 (2.88)	0.425	15.44 (2.97)	15.81 (3.02)	0.345	15.52 (2.95)
Gender (F/M)	54/16	105/47	52/22	0.458	12/3	58/21	141/61	0.625	149/52	49/30	0.045	
MMSE	29.04 (0.92)	28.99 (1.05)	28.76 (1.29)	0.215	29.07 (0.80)	29.05 (0.95)	28.90 (1.16)	0.513	28.87 (1.16)	29.09 (0.95)	0.129	28.95 (1.09)
Old-Old		***COMT***				***BDNF***				***APOE***		
	Met/Met	**Met/Val**	**Val/Val**	***p*-value**	**Met/Met**	**Met/Val**	**Val/Val**	***p*-value**	**ε4-**	**ε4+**	***p*-value**	
n	76	186	76	--	12	110	214	--	252	70	--	338
Age (years)	77.37 (4.82)	77.51 (4.55)	77.23 (5.01)	0.904	74.09 (2.59)	77.44 (5.05)	77.59 (4.56)	0.043	77.55 (4.81)	77.28 (4.35)	0.665	77.42 (4.71)
Education (years)	14.66 (3.20)	15.03 (2.81)	15.34 (3.06)	0.361	15.67 (2.46)	15.12 (2.93)	14.94 (3.00)	0.658	14.99 (2.96)	15.25 (3.13)	0.518	15.02 (2.96)
Gender (F/M)	47/29	120/64	44/32	0.547	6/6	70/40	135/79	0.648	155/97	44/26	0.827	
MMSE	28.42 (1.35)	28.49 (1.27)	28.36 (1.32)	0.780	29.25 (0.75)	28.52 (1.23)	28.36 (1.34)	0.053	28.50 (1.27)	28.20 (1.39)	0.098	28.44 (1.30)

Note. n = total number; *COMT = Catechol-O-methyl transferase*; *BDNF = Brain-derived neurotrophic factor*; *APOE = Apolipoprotein E*; $p < .05$. MMSE = Mini-Mental State Exam. Standard deviations are in parentheses. For the analyses involving the *APOE* genotypes, the ε2/ε4 carriers (n = 30) were deleted from the sample.

Table 6-3

Confirmatory factor analysis and longitudinal invariance model fit statistics and chi-square difference test for executive function factor by time point 1 to 3

	AIC	**BIC**	$\chi^2_M(df_M)$	**RMSEA (90% CI)**	**CFI**	**SRMR**	χ^2_D (df_D)
Confirmatory Factor Analysis							
T1	12263.880	12417.267	3.011 (2); p = 0.222	0.028 (0.00-0.089)	0.993	0.015	--
T2	10624.309	10675.332	0.239 (2); p = 0.887	0.000 (0.000-0.041)	1.000	0.004	--
T3	5738.166	5782.450	2.901 (2); p = 0.235	0.039 (0.000-0.129)	0.991	0.021	--
Longitudinal Invariance							
Configural	27666.008	27884.004	65.528 (41); p = 0.009	0.031 (0.016-0.044)	0.984	0.077	--
Metric	27661.656	27852.958	73.176 (47); p = 0.009	0.030 (0.015-0.042)	0.983	0.079	7.648 (6)
Scalar	27775.311	27939.920	198.832 (53); p = 0.000	0.066 (0.056-0.076)	0.906	0.104	125.656 (6)**
Partial scalar[a]	27669.082	27851.487	84.602 (49); p = 0.001	0.034 (0.021-0.046)	0.977	0.084	11.426 (2)*

Note. AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; χ^2_M = Chi-square test of model fit; df_M = Degrees of freedom for model fit; RMSEA = Root Mean Square Error of Approximation; CI = Confidence Interval; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; X^2_D = Chi-square test of difference; df_D = Degrees of freedom for difference in model fit; T = Time point.

*p<.05; **p<.001.

[a]Partial scalar, where the intercept for Hayling and Stroop were constrained to be equal across all three time points.

Table 6-4

Latent growth model fit statistics and chi-square difference test for executive function by age

Model	**H0 value**	**Free Parameters**	**-2LL**	**AIC**	**BIC**	$\boldsymbol{D\ (df_D)}$
Fixed Intercept	-2067.192	4	4134.384	4142.384	4160.180	--
Random Intercept	-1248.233	5	2496.466	2506.467	2528.711	1637.918 (1)
Random Intercept, Fixed Slope	-1229.368	6	2458.736	2470.736	2497.429	37.73 (1)**
Random Intercept, Random Slope	-868.207	8	1736.414	1752.413	1788.004	722.322 (2)**
Random Intercept, Random Slope, Fixed Quadratic	1263.880	9	2527.760	2545.760	2585.800	-791.346 (1)

Note. H0 = Log Likelihood; -2LL = -2 Log Likelihood; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; D = Deviance statistic; df_D = Degrees of freedom for difference in deviance statistics.
*p<.05; **p<.001.

Table 6-5

Regression coefficients and model fit indices by research question for all models examined at baseline and 9-year change on executive function

	Intercept			Slope			Model Fit Statistics				
Models	**β**	**SE**	***p***	**β**	**SE**	***p***	**H0 value**	**Free Parameters**	**-2LL**	**AIC**	**BIC**
Research question 1a											
Independent											
(a) COMT (*n* = 632)	0.015	0.063	0.816	0.002	0.003	0.496	-862.090	14	1724.18	1752.181	1814.465
(b) BDNF(*n* = 632)	-0.055	0.075	0.464	-0.003	0.004	0.469	-862.319	14	1724.638	1752.638	1814.923
(c) APOE (*n* = 602)	-0.206	0.098	0.036	-0.007	0.005	0.156	-827.278	14	1654.556	1682.557	1744.160
Age (YO versus OO)											
YO											
(a) *COMT* (*n* = 296)	-0.002	0.061	0.972	0.002	0.004	0.690	-542.049	28	1084.098	1140.099	1264.668
(b) BDNF (*n* = 296)	-0.045	0.073	0.541	-0.003	0.005	0.588	-541.309	28	1082.618	1138.617	1263.186
(c) APOE (*n* = 280)	-0.210	0.100	0.036	-0.015	0.007	0.020	-514.220	28	1028.44	1084.441	1207.648
OO											
(a) *COMT* (*n* = 336)	-0.023	0.073	0.753	-0.002	0.007	0.755	-542.050	28	1084.1	1140.099	1264.668
(b) BDNF (*n* = 336)	-0.020	0.092	0.830	0.003	0.009	0.699	-541.308	28	1082.616	1138.617	1263.185
(c) APOE (*n* = 322)	-0.197	0.116	0.089	-0.029	0.011	0.007	-514.220	28	1028.44	1084.440	1207.647
Lifestyle activities (Low versus High)											
High activities											
(a) *COMT* (*n* = 292)	0.080	0.098	0.412	0.006	0.004	0.175	-784.476	28	1568.952	1624.952	1749.164
(b) BDNF (*n* = 292)	-0.039	0.125	0.753	-0.002	0.005	0.705	-786.489	28	1572.978	1628.977	1753.189

Models	β	SE	*p*	β	SE	*p*	H0 value	Free Parameters	-2LL	AIC	BIC
(c) APOE (*n* = 279)	-0.215	0.144	0.134	-0.005	0.006	0.462	-751.822	28	1503.644	1559.644	1682.524
Low activities											
(a) *COMT* (*n* = 332)	-0.046	0.078	0.552	-0.004	0.005	0.444	-784.476	28	1568.952	1624.952	1749.164
(b) BDNF (*n* = 332)	-0.034	0.090	0.703	0.000	0.007	0.964	-786.489	28	1572.978	1628.977	1753.189
(c) APOE (*n* = 316)	-0.236	0.133	0.075	-0.011	0.009	0.205	-751.822	28	1503.644	1559.644	1682.524
Research question 1b											
***APOE* (ε4+)**											
(a) *COMT* (*n* = 149)	-0.177	0.152	0.243	-0.006	0.007	0.388	-815.111	28	1630.222	1686.222	1809.429
(b) BDNF (*n* = 453)	-0.373	0.179	0.037	-0.015	0.009	0.101	-814.361	28	1628.722	1684.721	1807.929
YO											
(a) *COMT* (*n* = 79)	-0.073	0.153	0.635	0.000	0.011	0.992	-113.884	28	227.768	283.768	385.543
(b) BDNF (*n* = 79)	-0.330	0.145	0.023	-0.032	0.010	0.002	-110.808	28	221.616	277.615	379.389
OO											
(a) *COMT* (*n* = 70)	-0.417	0.219	0.057	-0.030	0.024	0.197	-365.306	28	730.612	786.611	892.299
(b) BDNF (*n* = 70)	0.103	0.098	0.751	0.002	0.035	0.948	-364.416	28	728.832	784.831	890.519
High activities											
(a) *COMT* (*n* = 75)	-0.144	0.259	0.578	-0.001	0.012	0.951	-211.983	28	423.966	479.972	563.894
(b) BDNF (*n* = 75)	-0.525	0.252	0.037	-0.022	0.012	0.066	-211.659	28	423.318	479.318	563.240
Low activities											
(a) *COMT* (*n* = 73)	-0.200	0.235	0.394	-0.019	0.010	0.051	-211.983	28	423.966	479.972	563.894
(b) BDNF (*n* = 73)	-0.209	0.341	0.541	0.001	0.017	0.967	-211.659	28	423.318	479.318	563.240
***APOE* (ε4-)**											
(a) *COMT* (*n* = 453)	0.0603	0.071	0.371	0.004	0.004	0.208	-815.111	28	1630.222	1686.222	1809.429
(b) BDNF (*n* = 453)	0.052	0.085	0.537	0.002	0.004	0.639	-814.361	28	1628.722	1684.721	1807.929

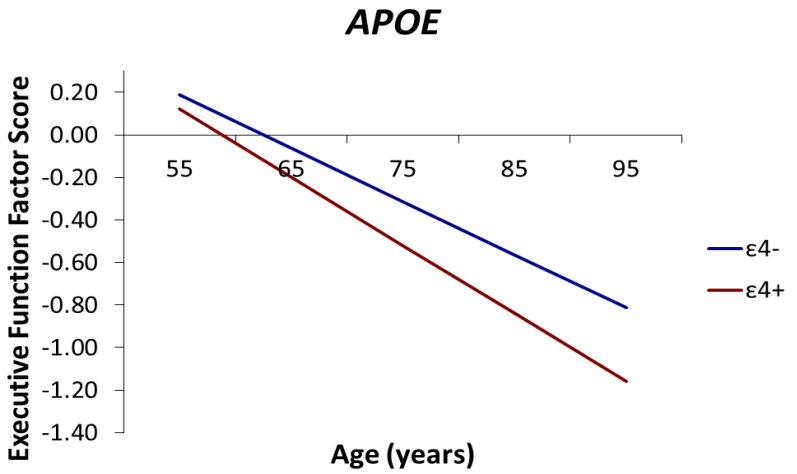
Models	β	SE	*p*	β	SE	*p*	H0 value	Free Parameters	-2LL	AIC	BIC
YO											
(a) *COMT* (*n* = 201)	0.033	0.069	0.636	0.005	0.004	0.230	-113.884	28	227.768	283.768	385.543
(b) BDNF (*n* = 201)	0.074	0.094	0.434	0.008	0.006	0.195	-110.808	28	221.616	277.615	379.389
OO											
(a) *COMT* (*n* = 252)	0.057	0.082	0.487	0.003	0.008	0.705	-365.306	28	730.612	786.611	892.299
(b) BDNF (*n* = 252)	-0.054	0.098	0.581	0.006	0.009	0.546	-364.416	28	728.832	784.831	890.519
High activities											
(a) *COMT* (*n* = 243)	0.141	0.102	0.167	0.008	0.004	0.084	-514.825	28	1029.65	1085.650	1200.521
(b) BDNF (*n* = 243)	0.118	0.136	0.389	0.005	0.006	0.345	-515.885	28	1031.77	1087.770	1202.642
Low activities											
(a) *COMT* (*n* = 204)	-0.013	0.089	0.882	-0.001	0.006	0.932	-514.825	28	1029.65	1085.650	1200.521
(b) BDNF (*n* = 204)	0.037	0.094	0.692	0.000	0.008	0.965	-515.885	28	1031.77	1087.770	1202.642
Research question 2a											
Additive											
(a) *COMT* + *BDNF* (*n* = 632)	-0.014	0.048	0.774	0.000	0.002	0.976	-862.379	14	1724.758	1752.758	1815.042
(b) *COMT* + *APOE* (*n* = 602)	-0.051	0.056	0.362	-0.001	0.003	0.830	-828.486	14	1656.972	1684.972	1746.575
(c) *BDNF* + *APOE* (*n* = 602)	-0.106	0.057	0.063	-0.004	0.003	0.170	-828.153	14	1656.306	1684.307	1745.910
Age (YO versus OO)											
YO											
(a) *COMT* + *BDNF* (*n* = 296)	-0.018	0.046	0.690	0.000	0.003	0.976	-541.708	28	1083.416	1136.417	1263.986
(b) *COMT* + *APOE* (*n* = 280)	-0.058	0.056	0.302	-0.003	0.004	0.464	-518.897	28	1037.794	1093.794	1217.001
(c) *BDNF* + *APOE* (*n* = 280)	-0.102	0.057	0.074	-0.007	0.004	0.070	-518.641	28	1037.282	1093.282	1216.489
OO											
(a) *COMT* + *BDNF* (*n* = 336)	-0.022	0.062	0.719	0.000	0.006	0.971	-541.709	28	1083.418	1136.417	1263.986
(b) *COMT* + *APOE* (*n* = 322)	-0.078	0.064	0.224	-0.010	0.006	0.103	-518.897	28	1037.794	1093.794	1217.001
(c) *BDNF* + *APOE* (*n* = 332)	-0.087	0.069	0.205	-0.007	0.006	0.292	-518.641	28	1037.282	1093.282	1216.489

Models	β	SE	*p*	β	SE	*p*	H0 value	Free Parameters	-2LL	AIC	BIC
Lifestyle activities (Low versus High)											
High activities											
(a) *COMT* + *BDNF* (*n* = 292)	0.034	0.081	0.671	0.003	0.004	0.421	-785.597	28	1571.194	1627.193	1751.193
(b) *COMT* + *APOE* (*n* = 279)	-0.013	0.082	0.870	0.002	0.004	0.492	-752.085	28	1504.17	1560.171	1683.051
(c) *BDNF* + *APOE* (*n* = 279)	-0.116	0.088	0.190	-0.003	0.004	0.389	-753.875	28	1507.75	1563.750	1686.630
Low activities											
(a) *COMT* + *BDNF* (*n* = 332)	-0.038	0.054	0.484	-0.002	0.004	0.610	-785.597	28	1571.194	1627.193	1751.193
(b) *COMT* + *APOE* (*n* = 316)	-0.105	0.074	0.156	-0.007	0.005	0.135	-752.085	28	1504.17	1560.171	1683.051
(c) *BDNF* + *APOE* (*n* = 316)	-0.093	0.075	0.213	-0.003	0.005	0.549	-753.875	28	1507.75	1563.750	1686.630
Research question 2b											
***APOE* (ε4+)**											
COMT + *BDNF* (*n* = 149)	-0.307	0.123	0.013	-0.012	0.006	0.054	-812.822	28	1625.644	1681.643	1804.850
YO											
COMT + *BDNF* (*n* = 79)	-0.187	0.120	0.120	-0.013	0.009	0.146	-111.958	28	223.916	279.915	381.689
OO											
COMT + *BDNF* (*n* = 70)	-0.299	0.235	0.203	-0.025	0.023	0.280	-366.376	28	732.752	788.753	894.440
High activities											
COMT + *BDNF* (*n* = 75)	-0.322	0.224	0.150	-0.010	0.010	0.347	-212.266	28	424.532	480.531	564.453
Low activities											
COMT + *BDNF* (*n* = 73)	-0.283	0.214	0.186	-0.015	0.009	0.110	-212.266	28	424.532	480.531	564.453
***APOE* (ε4-)**											
COMT + *BDNF* (*n* = 453)	0.056	0.051	0.275	0.003	0.003	0.221	-812.822	28	1625.644	1681.643	1804.850
YO											

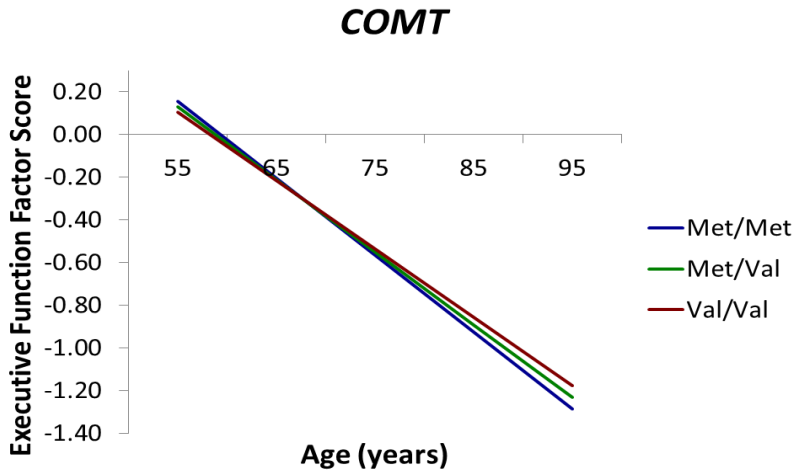
Models	β	SE	*p*	β	SE	*p*	H0 value	Free Parameters	-2LL	AIC	BIC
COMT + *BDNF* (*n* = 201)	0.046	0.051	0.365	0.006	0.003	0.080	-111.958	28	223.916	279.915	381.689
OO											
COMT + *BDNF* (*n* = 252)	0.010	0.066	0.881	0.004	0.006	0.491	-366.376	28	732.752	788.753	894.440
High activities											
COMT + *BDNF* (*n* = 204)	0.149	0.083	0.072	0.008	0.004	0.046	-514.224	28	1028.448	1084.448	1199.320
Low activities											
COMT + *BDNF* (*n* = 243)	0.007	0.056	0.896	0.000	0.004	0.978	-514.224	28	1028.448	1084.448	1199.320

Note. YO = Young-old; OO = Old-old; Low activities = Low lifestyle activities; High activities = High lifestyle activities; Est. = Regression Estimate; SE = Standard Error; H0 = Log Likelihood; -2LL = -2 Log Likelihood; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria. *COMT = Catechol-O-methyltransferase*; *BDNF = Brain-derived neurotrophic factor*; *APOE = Apolipoprotein E*.

(a)



(b)



(c)

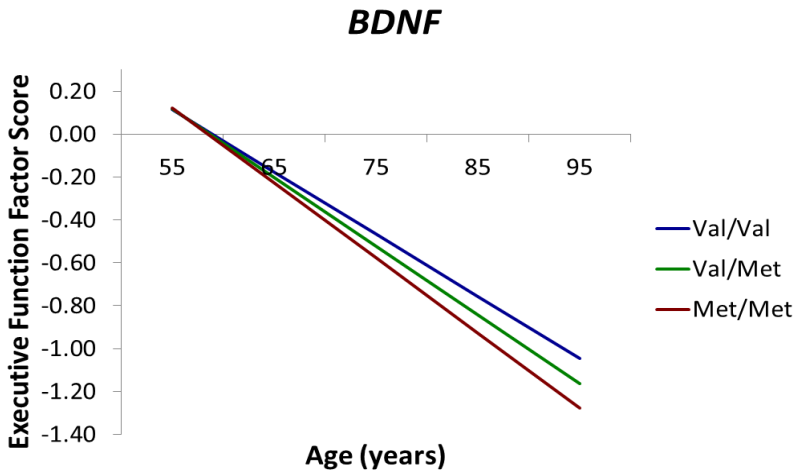


Figure 6-1. (a) *APOE* ε4+ carriers performed worse than their non-risk counterparts (ε4-) at age 75 on EF. EF decline (slope) was not significantly different between the two groups (ε4+ versus ε4-). Independent effects were not observed with the (b*) COMT* or (c) *BDNF* allelic risk on EF performance or change.

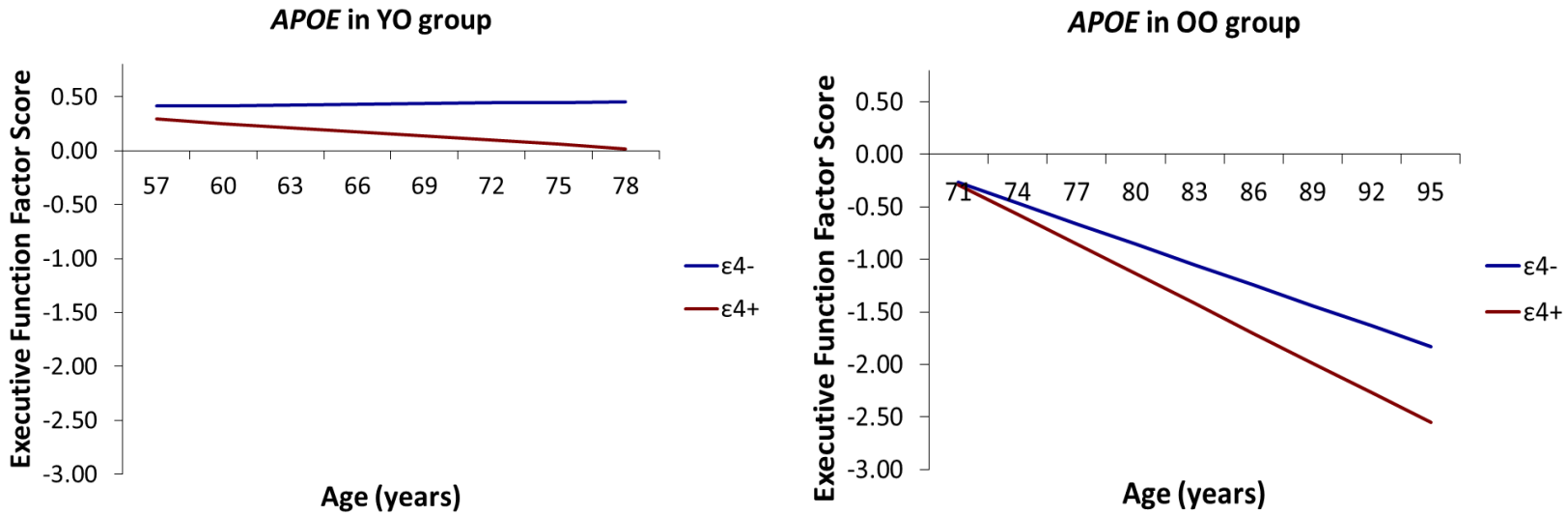


Figure 6-2. In the young-old (YO) group, *APOE* ε4+ carriers performed worse than their non-risk (ε4-) counterparts at age 63 years and had steeper 9-year decline in EF performance than their non-risk counterparts (ε4-). In the old-old (OO) group, *APOE* ε4+ carriers showed steeper 9-year decline on EF than their non-risk counterparts.

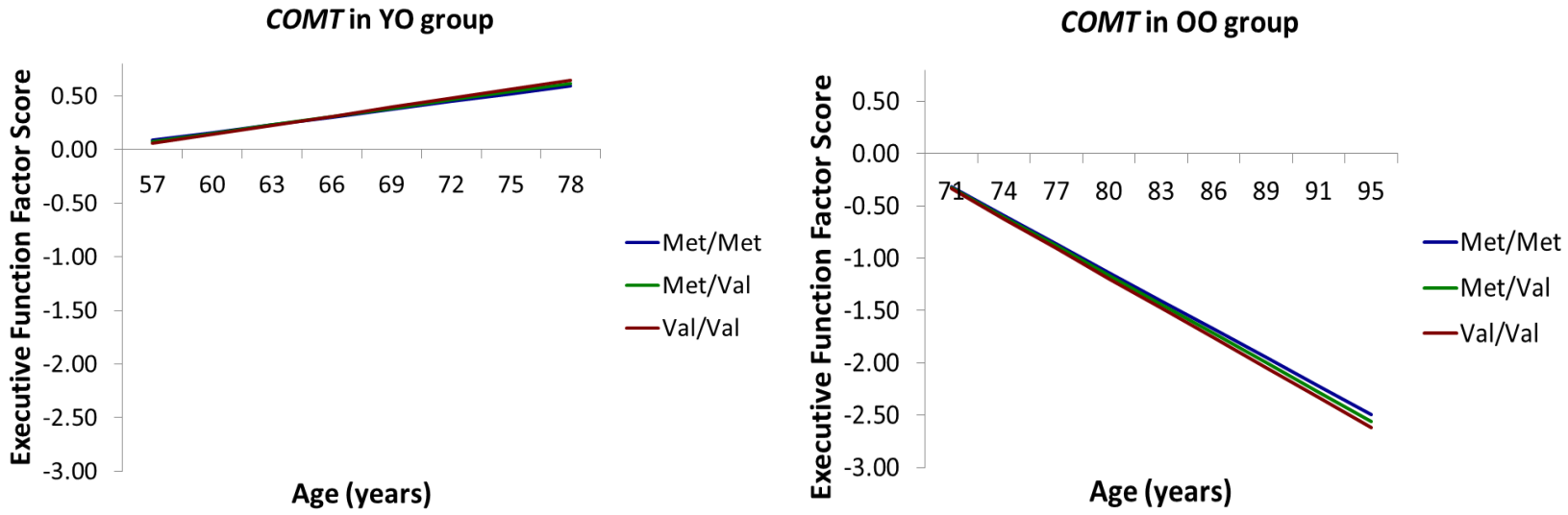


Figure 6-3. COMT genotype did not significantly influence EF performance or change in the young-old (YO) group or the old-old (OO) group. However, adults in the OO group showed EF decline compared to adults in the YO group, showing an overall age effect.

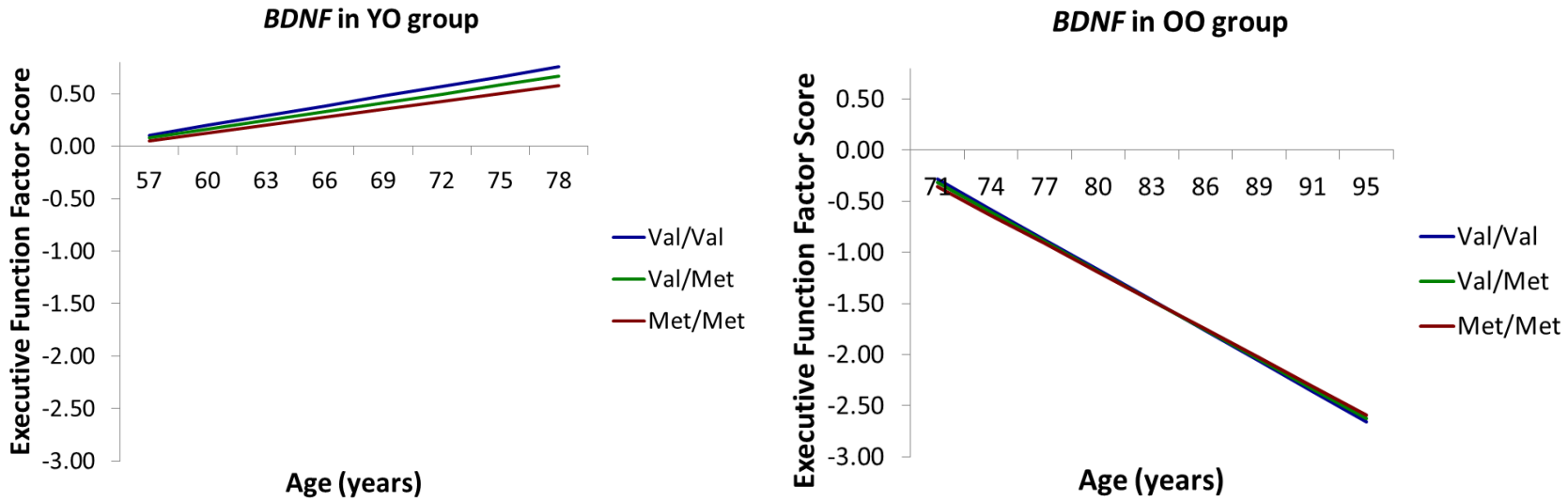


Figure 6-4. BDNF genotype did not significantly influence EF performance or change in the young-old (YO) group or the old-old (OO) group. However, adults in the OO group showed EF decline compared to adults in the YO group, showing an overall age effect.

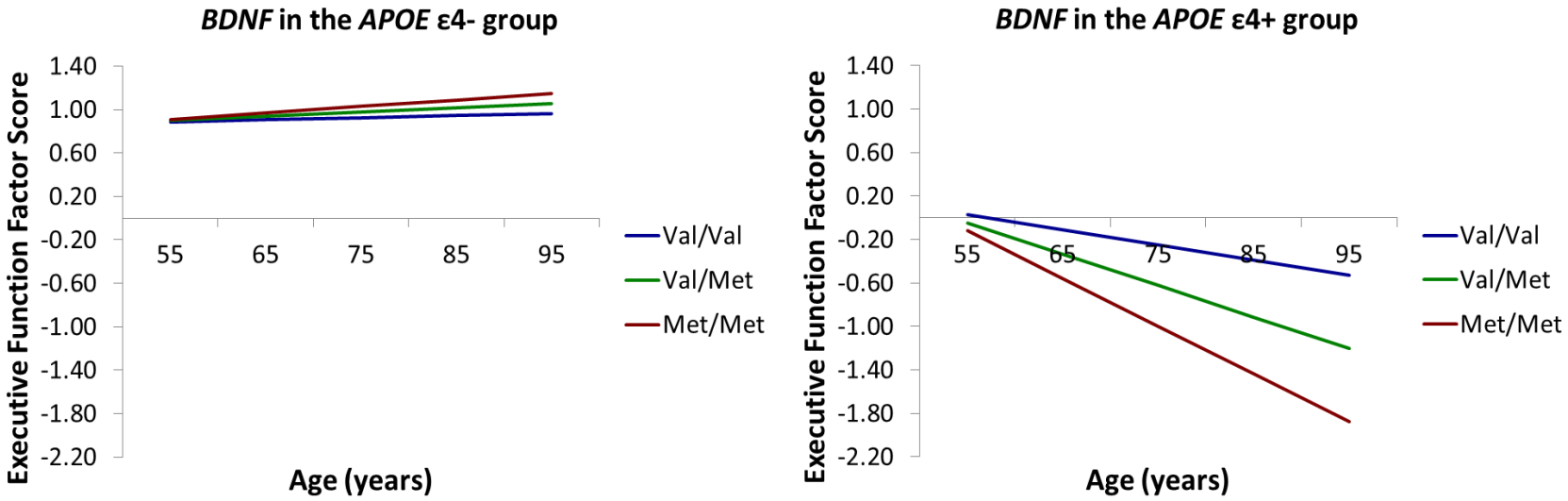


Figure 6-5. In the *APOE* ε4+ group, *BDNF* Met/Met homozygotes had the worst EF performance compared to their non-risk counterparts (Val/Val homozygotes) at age 75 years. In contrast, in the *APOE* ε4- group, *BDNF* genotype did not show difference in EF performance.

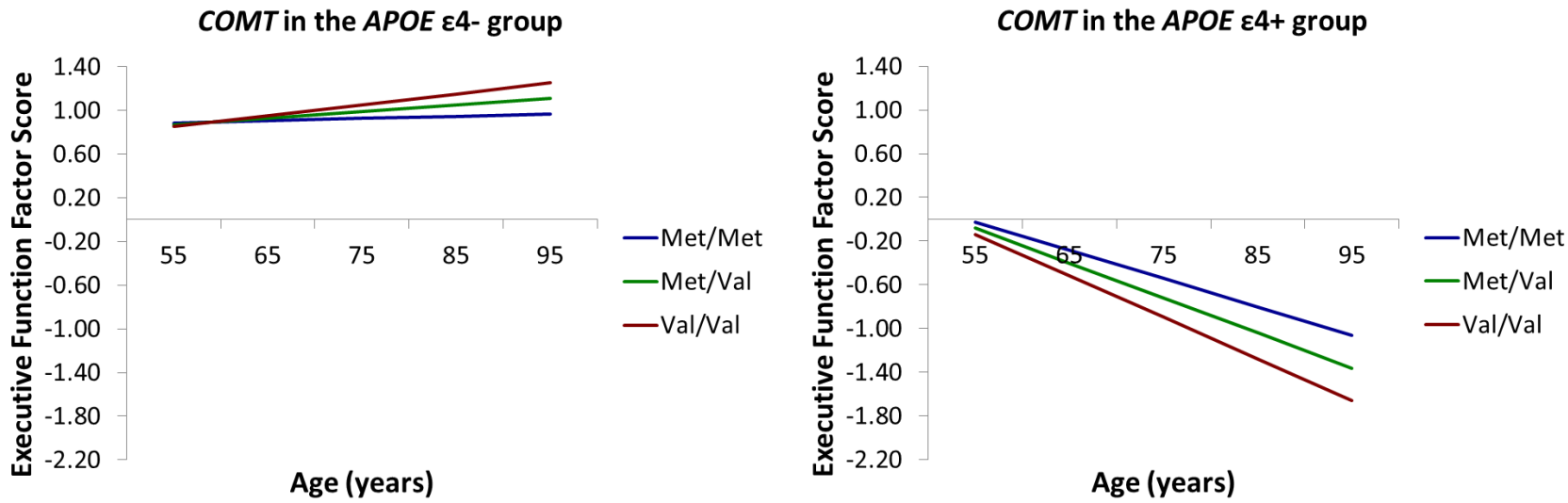


Figure 6-6. COMT genotype did not significantly influence EF performance or change in the *APOE* ε4- or ε4+ group. However, adults in the *APOE* ε4+ group showed an overall EF decline compared to adults in the *APOE* ε4- group regardless of *COMT* genotype.

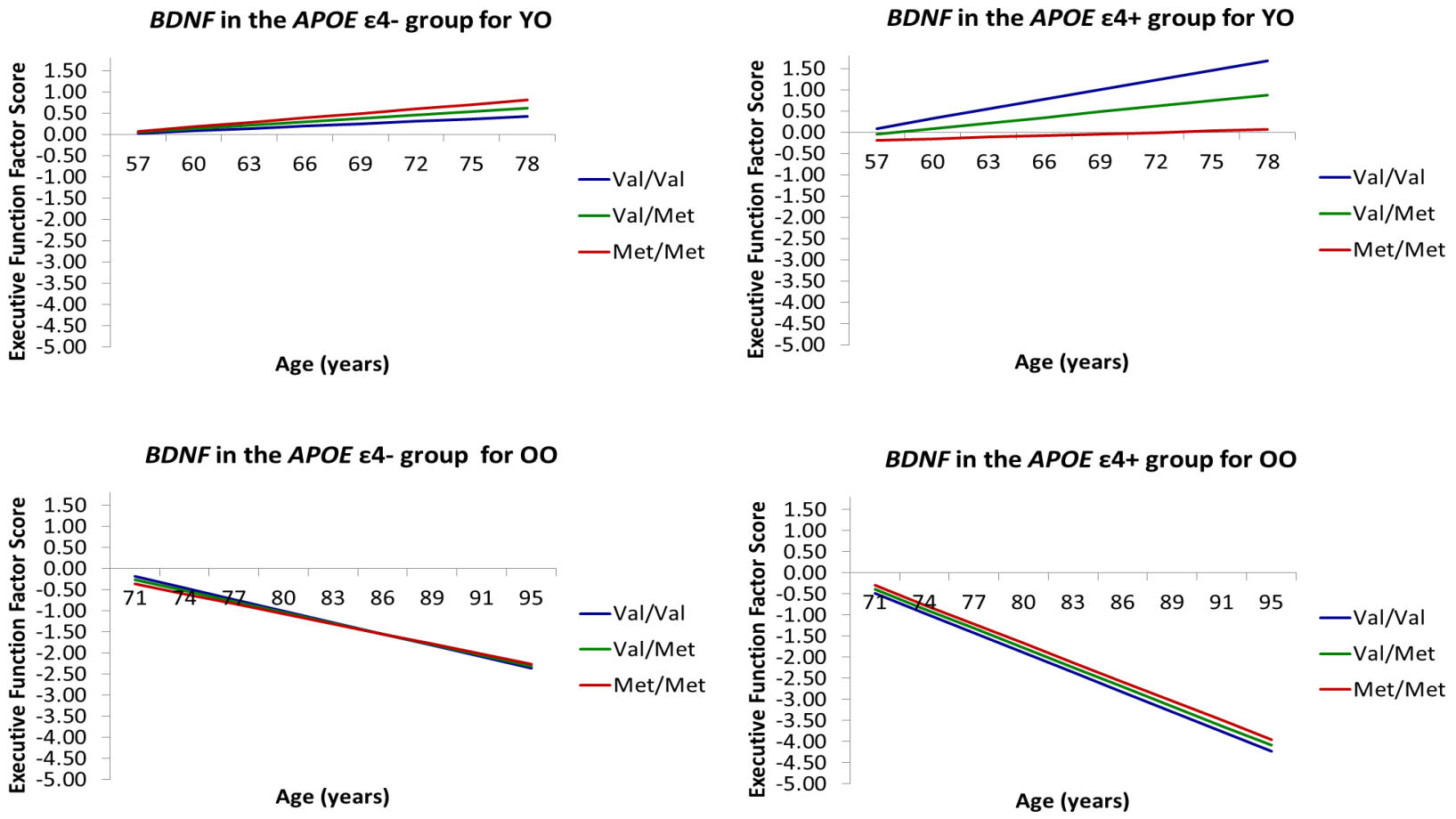


Figure 6-7. First, a significant *BDNF* genotype effect was observed in the *APOE* ε4+ group for young-old (YO) adults. Specifically, *BDNF* no risk (Val/Val) homozygotes had the best EF performance at age 75 and less steep decline compared with their risk counterparts (Met + carriers). Second, there was no significant *BDNF* genotype difference in the old-old (OO) groups or the *APOE* ε4- group for EF performance or change. Third, an overall age effect was observed, where OO adults were declining in EF performance compared to the YO adults.

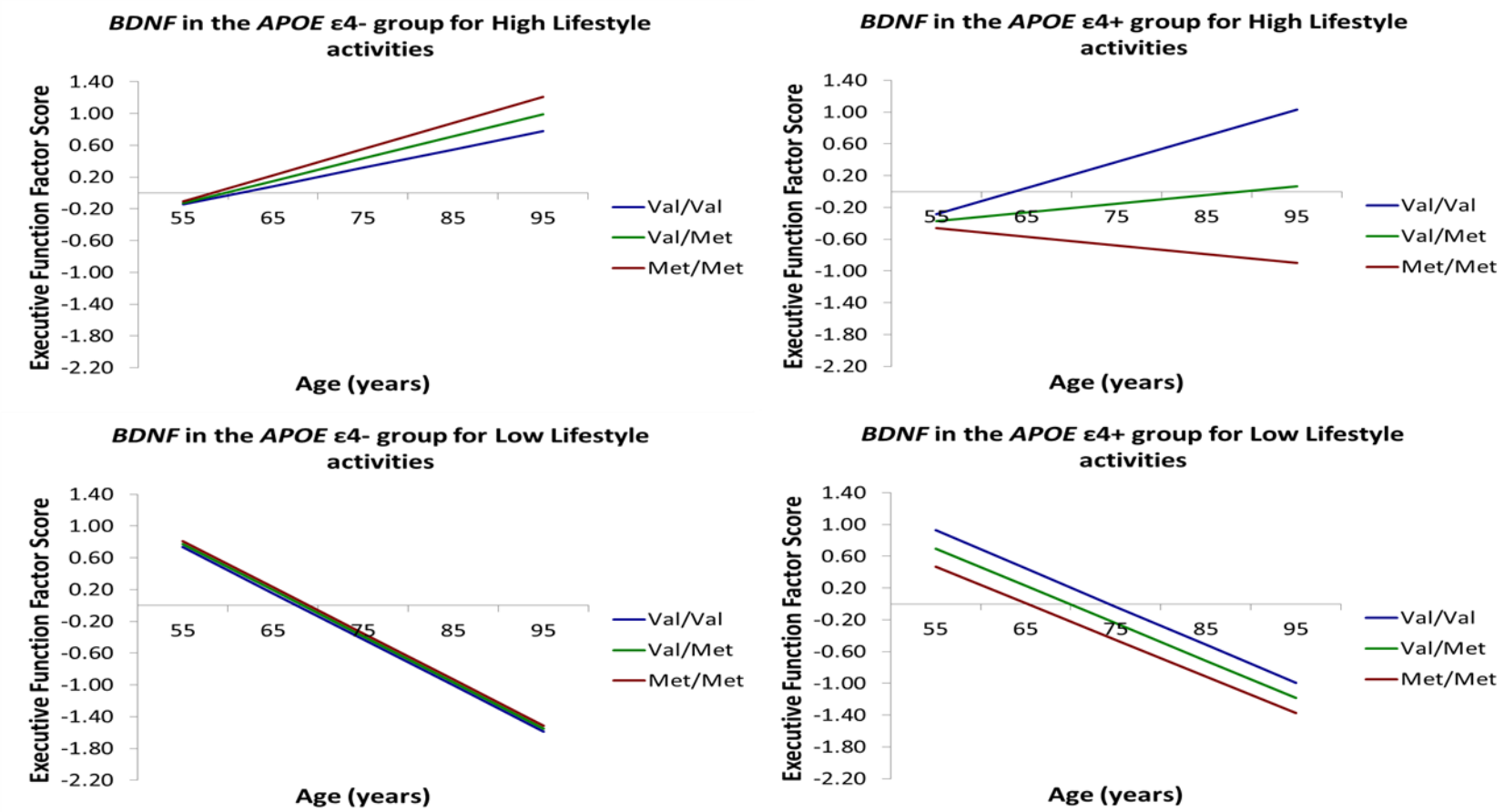


Figure 6-8. First, a significant *BDNF* genotype effect was observed in the *APOE* ε4+ group for adults in the high lifestyle activities group. Specifically, *BDNF* risk (Met/Met) homozygotes had the worst EF performance at age 75 compared with their non-risk counterparts (Val/Val homozygotes). Second, there was no significant *BDNF* genotype difference in the low lifestyle activities groups or the *APOE* ε4- group. Third, an overall lifestyle effect was observed, where adults in the low lifestyle activities group were declining in EF performance compared to the adults in the high lifestyle activities group.

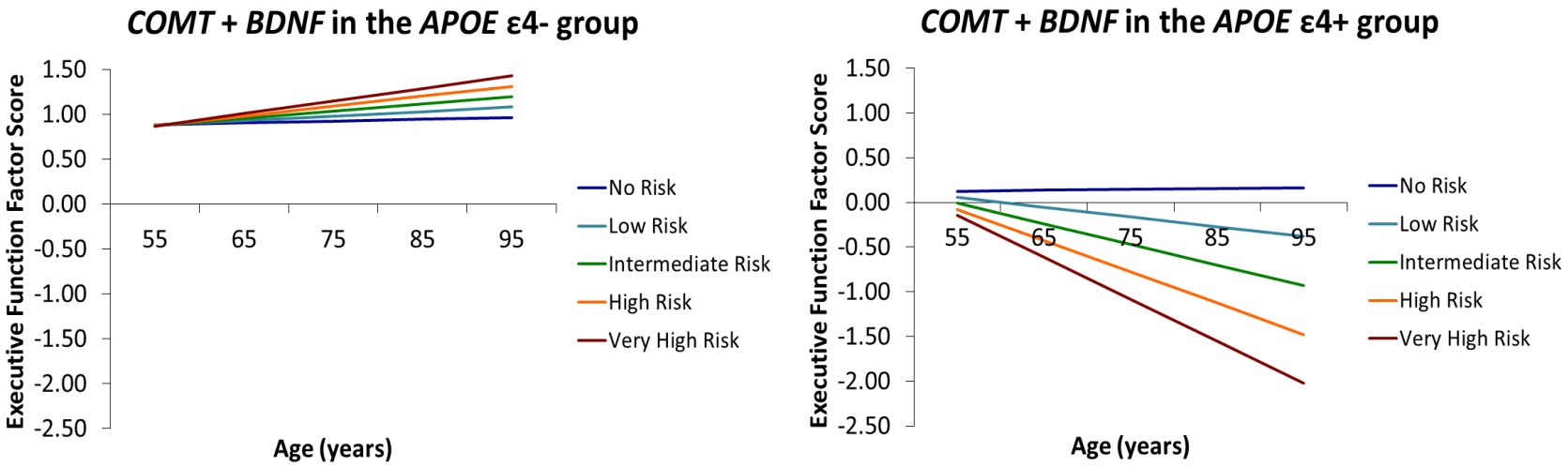


Figure 6-9. APOE effect modification was observed for *COMT* + *BDNF* additive effect on EF performance. *APOE* ε4+ carriers had poorer EF performance with increasing allelic risk in the *COMT* + *BDNF* risk panel at age 75 years and borderline 9-year decline. In contrast, *APOE* ε4- group was protected from the deleterious effect on EF performance and decline with increasing allelic risk in the *COMT* + *BDNF* risk panel.

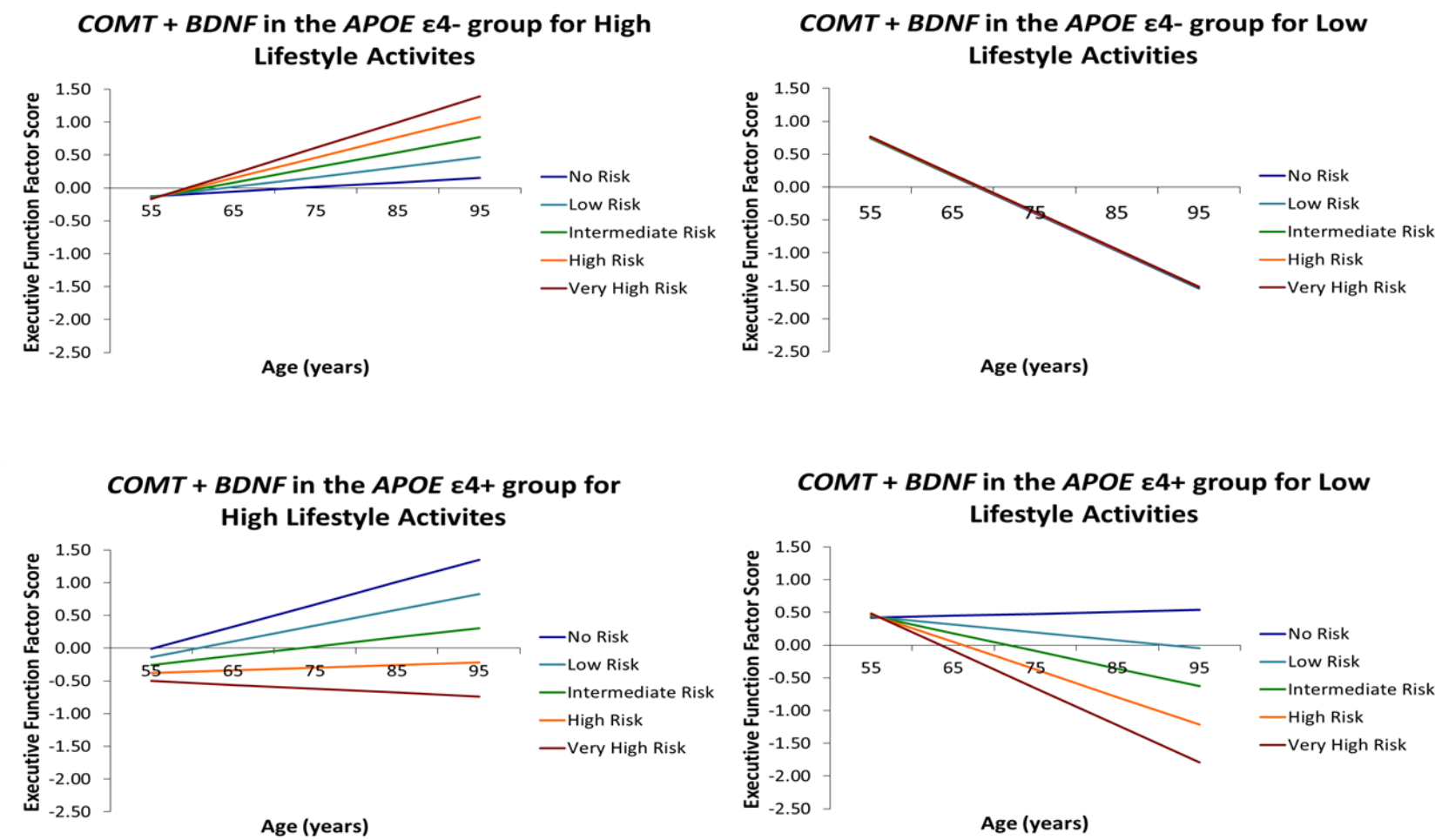


Figure 6-10. First, in the *APOE* ε4- group, adults with high lifestyle activities were protected from the decline associated with increasing allelic risk in the *COMT* + *BDNF* risk panel with age on EF performance. In contrast, those with low lifestyle activities showed an overall decline in EF performance. Second, there was no significant difference in EF performance and change with increasing allelic risk in the *COMT* + *BDNF* risk panel for *APOE* ε4+ carriers with high or low lifestyle activities.

CHAPTER 7: GENERAL DISCUSSION AND CONCLUSION

The overall purpose of this dissertation was to examine associations of both non-modifiable (i.e., genetic) and modifiable (i.e., demographic, health, lifestyle) risk factors on concurrent and longitudinal neurocognitive performance (i.e., executive function [EF], episodic memory [EM]) and clinical status (Mild Cognitive Impairment [MCI]). Two specific and related goals were pursued. First, I intended to develop a sensitive and simple index that used multi-domain information to calculate risk scores for predicting EM performance and change over a 40-year band of aging. As a corollary and further test of my approach to risk score calculation, I evaluated the extent to which these risk scores distinguished non-demented (normal aging) older adults from those with MCI. Second, I sought to test selective gene interactive versus additive associations to examine potential underlying mechanisms of genetic influences on EF performance and change in non-demented older adults. To address these goals, I divided the dissertation work into three related studies. I turn now to a critical review of each of these studies in terms of the approach, main results, significance, and pertinence to the goals.

The first goal was operationalized with Study 1 (see Chapter 4). Study 1 examined genetic, demographic, health, and lifestyle risk factors to build, compare, and validate a multi-domain risk index for cognitive impairment in aging. Several novel statistical analyses were applied in Study 1 including latent growth models (LGM) and formative genetic risk models. LGM uses independent and dependent variables concurrently in the same model to determine developmental trajectories, and individual differences and change (Duncan & Duncan, 2009). A formative model represents indicators as predictors for the latent composite and regression coefficients are estimated to explain variances in the composite score (Kline, 2013). Study 1 was divided into two parts, Study 1a and Study 1b, to account for differences in statistical analyses

and the methods applied to build the multi-domain risk score. The main difference was that Study 1a used modifiable risk factor scores in a LGM and Study 1b used both non-modifiable and modifiable risk factor scores to predict EM performance and change. In addition, Study 1b tested how well the risk score distinguished clinical status (non-demented versus MCI). I now describe both parts of Study 1 and their significance.

Study 1a examined modifiable risk factors to predict EM performance and 9-year change. Demographic (i.e., age, gender, education, marital status) and health (i.e., diabetes, depression, heart disease, stroke, hypertension, hardening of arteries, alcohol dependence, tobacco dependence, traumatic brain injury) composites, and latent lifestyle factor (i.e., physical and social activities, novel and integrative information processing) were included in a parallel process LGM. As expected, higher risk scores on all three independent risk factors predicted worse EM performance at age 75 years and steeper 9-year decline. A combined high risk score on all three risk factors showed the greatest fanning effect between low, intermediate, and high risk scores at age 75 years and across the 40-year age band. The fanning effect (see Figure 4-6) showed that a combined risk score from all three risk factors resulted in a larger effect on EM performance and change because the distribution between combined low, intermediate, and high risk scores were much greater (i.e., greatest fanning effect) than any independent (i.e., demographic, health, lifestyle) low, intermediate, and high risk score. This means that all three risk factor scores in synergy had the largest impact on EM performance and change. As expected, the difference between low, intermediate, and high risk score is greater for a combined risk score than an independent risk score. For example, an adult with a combined low risk score would have a higher EM performance at age 75 years and less 9-year decline compared to an adult who has a low risk score on only two out of the three risk factors (see Figure 4-5). If only

one modifiable risk factor is managed at a low risk score, then the deleterious association with EM performance would be significantly reduced compared to a combined high risk score on all three risk domains.

I now move to the second part of this study, Study 1b, which takes into account non-modifiable risk factors. Study 1b used categorical groupings to develop an overall risk score that examined two cognitive aging (i.e., *COMT*, *BDNF*) and four AD-related (i.e., *APOE*, *CLU*, *CR1*, *PICALM*) genes as well as demographic, health, and lifestyle factors. First, independent and different combination of risk scores were examined to predict EM performance and 9-year change. Higher risk scores on independent and cumulative (additive) risk for demographic, health, lifestyle, and genetic factors predicted worse EM performance at baseline and time point 3. I did not observe a more deleterious effect on EM performance and decline with additive risk scores (as expected) compared to independent risk scores. Although categorical groupings and additive approach may be a simple and easy to apply in large datasets, the synergistic effect of multiple risk domains (i.e., genetic and modifiable risk factors) may not be through simple cumulative mechanisms. None of the five variations of genetic risk scores examined (6 gene standard, 4 AD gene standard, *APOE*, 6 gene formative, 4 AD gene formative) were associated with EM performance or decline. This means that the 6 gene and 4 AD gene risk scores do not function via additive mechanisms, but may work through other pathways. My findings imply that the underpinnings of both genetic and modifiable risk factors on EM performance and change may not be simple additive effects in typically normal aging older adults. Past studies have reported acceptable c-statistics for dementia prediction in clinical settings (Kivipelto et al., 2006) with additive scores. This is the first study to show that complex neurobiological mechanisms associated with cognitive impairment may be more multiplex in the pre-clinical stages and not as

straight forward as in the later dementia stages (Anstey et al., 2014). In addition, I observed that risk factor trajectories over the 9-year period did not predict EM change. This finding implies that the length of exposure to risk factors may not be as important for older adult groups as exposure to independent risk factors alone. This means that risk reduction overall may be an appropriate and suitable method for older adults with no signs of cognitive impairment than focusing on the length of exposure.

Second, both independent and additive risk scores were used to distinguish non-demented older adults from those classified as MCI. Despite my expectations, c-statistics for additive risk scores were in the unacceptable range (close to 0.50), but independent risk score for demographic ($c = 0.62$) and health ($c = 0.37$) risk domains significantly distinguished non-demented older adults from MCI adults. Specifically, higher demographic and lower health risk scores were present in the MCI group. Although I expected to observe higher health risk scores in the MCI group, my findings show that health factors in old age may work through other pathways that were not addressed in this study. For example, MCI older adults may have lower blood pressure levels (health predictor) which may act via decreased cerebral blood flow with increasing age.

I addressed one important aspect of synergistic risk scores (i.e., additive associations). Although past studies have used additive risk scores to predict dementia status (i.e., AD) (Anstey et al., 2014; Kivipelto et al., 2006), my results suggest that predicting EM decline in normal aging may not be through the same underlying mechanisms of influence. Past studies may also have been vulnerable to elevated effect of risk scores because the population was derived from clinical settings with higher dementia prevalence (Kivipelto et al., 2006). Overall, it is imperative to reduce (a) disease burden (i.e., health risk), (b) lifestyle risk, and (c) modifiable demographic

risk predictors, as early as possible (in the pre-clinical phase) to decrease EM decline and ultimately delay or prevent dementia onset. Until risk factors are validated in this field through randomized control trials and animal models to build risk assessment tools that target synergistic mechanisms of risk factors, increasing protective factors and reducing risk factors across multiple domains in typically normal aging adults may be the most sensible and effective method to the address the global dementia epidemic.

The second goal was operationalized with Study 2 (see Chapter 5) and Study 3 (see Chapter 6). Study 2 examined independent, interactive, and additive associations of *COMT* and *BDNF*, and as stratified by *APOE* risk (ε4+) on EF performance in normal aging. Selective additive effects of *COMT*, *BDNF,* and age produced significant results. As expected, older adults with a high-risk allelic (*COMT* [Val/Val] + *BDNF* [Met/Met]) combination performed differentially worse on EF compared to their non-risk counterparts (*COMT* [Met/Met] + *BDNF* [Val/Val]). My findings support magnification of genetic (i.e., *COMT* + *BDNF*) effects on EF performance in old age. Previous studies have shown varying and inconsistent results with genetic magnification hypothesis for interactive effects. For example, a recent study showed that dopamine levels modulate NMDA receptor activity to influence EM in old age (Papenburg et al., 2014). My findings expand upon previous studies (Nagel et al., 2008; Wishart et al., 2010) and show that the underlying mechanism for *COMT* and *BDNF* synergistic associations on EF may not be through interactive effects. Specifically, there may be two separate *COMT* and *BDNF* pathways that influences EF performance. Increased allelic risk may only add towards the overall risk but the two pathways do not moderate or interact with dopamine or neurotrophic levels. Furthermore, only the *COMT* and *BDNF* additive effect was modified by *APOE* ε4. Specifically, adults with ε4 allele were at an increased EF performance vulnerability. This finding implies that

COMT + *BDNF* panel effect on EF may further be as a result of *APOE* ε4 effect modification. This leads to Study 3, which focused on independent and additive associations of *COMT*, *BDNF*, and *APOE* as moderated by age (young-old [YO] versus old-old [OO]) and lifestyle activities (high versus low) groups on EF performance and 9-year change. Findings in Study 3 provided additional support for *COMT* + *BDNF* additive associations and *APOE* ε4 effect modification. I observed that *APOE* ε4+ carriers magnified *COMT* + *BDNF* panel effect on EF performance at age 75 years but this effect was not present in the high lifestyle activities group. This suggests that *APOE* ε4 carriers with increasing *COMT* + *BDNF* allelic risk panel effect on EF performance may be intensified through lower lifestyle activities. Non-demented older adults with high genetic risk may benefit the most from risk moderating activities such as a high level of lifestyle activities. Taken together (*COMT* and *BDNF*) in Study 3, I replicated that reducing risk for one does not change or influence the risk associated with the other *COMT* or *BDNF* genetic allelic risk for *APOE* ε4+ carriers. Although only borderline significant, I also observed that this risk panel effect influences EF decline over 9 years.

In sum, there were four key findings in this dissertation. First, targeting adults in the combined high risk score group (from Study 1a) may be a useful strategy to use in randomized control trials aimed at modifiable risk factors for cognitive decline. Study 1a applied a LGM approach, which takes large numbers of risk predictors and a complex dataset to represent a simplified latent factor. This analysis accounts for growth and change in both predictors (i.e., lifestyle latent factor) and EM performance. This approach can identify adults at low, intermediate, and high risk for EM decline with increasing age as determined by independent or multiple risk domains. As EM impairment may be a cardinal pre-clinical marker for dementia (i.e., Alzheimer's disease [AD]) (Bäckman, Jones, Berger, Laukka, & Small, 2004), a low risk

score on all three modifiable risk factors should be a paramount objective for older adults with poor EM performance and decline.

Second, the multi-domain risk score in Study 1b expands the growing literature on dementia risk indices to include genetic risk factors and pre-clinical cognitive markers (i.e., EM decline). I examined multiple domains simultaneously to test synergistic (i.e., additive) associations on EM performance and decline. By adopting this method, researchers and clinicians can conduct an overall risk profile assessment at the pre-clinical stage. Such an assessment may be an essential and empirical approach to delaying cognitive impairment (or dementia onset) in typical aging older adults and developing efficacious clinical guidelines for risk reduction and dementia prevention in the future. The more cognizant older adults are about their health and lifestyle activities, the more likely they will adopt changes to reduce risk factors. Although multiple domains were included in the overall risk score, to expand this to clinical practice, future research needs to focus on quantity or amount required to reduce risk factors or increase protective factors in intervention studies.

Third, in Study 2 and Study 3, I systematically separated the synergistic associations of *COMT*, *BDNF*, and *APOE* (second goal) on a polygenic cognitive phenotype. Specifically, that (a) *COMT* and *BDNF* may influence EF performance via additive but not interactive effects and (b) *APOE* ε4 effect modification may only be present in *COMT* + *BDNF* additive associations. Regarding the possible mechanisms with independent, interactive, and additive associations for *COMT* and *BDNF* allelic risk influence on neurocognitive performance in normal aging (Nagel et al., 2008; Wishart et al., 2011), only high allelic risk for *COMT* + *BDNF* was associated with poorer EF performance at baseline. Study 2 is the first study to investigate interactive versus additive associations of *COMT* and *BDNF*, and *APOE* effect modification. My findings provide

a novel approach to examine synergistic associations of *COMT* and *BDNF* in relation to *APOE*. Overall, this research expanded the field of single candidate gene studies by examining the synergistic associations of genes, which may increase prediction accuracy of older adults at a high risk for EF impairment.

Fourth, in Study 3, I observed that older *APOE* ε4+ carriers who maintain a high level of everyday lifestyle activities may be protected from the deleterious effects of *COMT* + *BDNF* on EF performance. Regarding possible neurobiological underpinnings (second goal) for *COMT*, *BDNF*, and *APO*E in non-demented older adults, *APOE* ε4+ carriers with one protective allele for *COMT* or *BDNF* may only reduce the risk associated with that gene but may not change the allelic risk associated with the other *COMT* or *BDNF* gene. This research supports both a brain resource modulation (Lindenberger et al., 2008) and genetic aging magnification (Nagel et al., 2008) hypothesis and highlights a potential mechanism through which dopamine (*COMT*) and neurotrophic (*BDNF*) levels may be modified in *APOE* ε4+ carriers to simultaneously influence EF performance in old age. More importantly, my research shows that this cumulative and effect modification pathway can be moderated through lifestyle activities. Healthy lifestyle that includes high levels of social and physical activities, and novel and integrative information processing tasks may ameliorate and produce more favorable cognitive phenotypes for those with a high genetic allelic risk combination.

I now turn to future directions for the research and findings in this dissertation. First, applying a multi-domain approach to build and validate risk assessment tools for healthy aging older adults may help identify adults at a high cognitive impairment risk in the pre-clinical phase. Earlier identification and intervention programs will provide older adults the opportunity to make significant life changes towards a healthier lifestyle. The current risk score predicted a cardinal

marker of dementia, EM performance. Other neurocognitive domains may be associated with both genetic and non-modifiable risk factors. These include neurocognitive speed, which has been previously associated with genetic (McFall et al., 2015) and health (i.e., Type 2 diabetes; see Yeung, Fisher, & Dixon, 2009) risk factors in non-demented adults. Future dementia risk prevention trials may benefit from examining a multi-domain and individually tailored risk score approach (Olanrewaju, Clare, Barnes, & Brayne, 2015) to identify older adults at a high risk for cognitive impairment and delay dementia onset. An important question regarding the possible mechanisms for how all risk domains concurrently impact each adult differentially still remains to be investigated and answered.

Second, to be most useful in delaying dementia onset, future studies need to assemble risk assessment tools that target synergistic or cascading effect of risk factors to identify older adults with small and subtle signs of cognitive decline. This includes applying different statistical methods to maximize identification and prediction for those at a high risk is important. The formative genetic risk model introduced in this dissertation should be applied in future studies with other genotypes to examine formative versus standard genetic risk scores in cognitive aging. Although, I only tested the formative model with EM performance, future studies may find more favorable and expected results with other neurocognitive domains or risk factors.

Third, future studies should examine *COMT* + *BDNF* additive risk associations in non-demented older adults in the presence of (a) other cognitive aging genes, (b) modifiable risk factors, and (c) synergistic associations of dementia-related genes. My *COMT* + *BDNF* finding as modified by *APOE* genotype, allows researchers to build upon and examine the influence of other dementia-related genes to further develop the potential mechanisms of normal cognitive aging trajectories. This will give researchers the opportunity to identify adults at a high risk for

MCI or dementia much earlier. This will also provide risk assessment tools to examine specific risk factors and their synergistic associations to differentiate the underlying mechanisms that predicts normal decline versus impairment or dementia in the future. For example, AD genetic polymorphisms identified in genome wide association studies (i.e., *Clusterin, Complement receptor 1, Phosphatidylinositol binding clathrin assembly protein*; see Harold et al., 2009) may influence each other through select combination of synergistic associations (additive, interactive, and modification effects). AD-related genes may also influence dopaminergic and neurotrophic related genes to alter cognitive aging trajectories in non-demented older adults.

Fourth, replicating the findings in this research with diverse populations including (a) younger (20-40 years old) or middle aged (41-50 years old) adults and (b) those at high risk for dementia, is an important next step. Although I included a 40-year band of aging, validating the findings in younger populations may allow researchers to predict cognitive decline 20-30 years earlier. In addition, by identifying common risk factors between those at a high risk for dementia and younger non-demented older adults may depict the underlying changes that occur with aging. Furthermore, informing young and middle aged adults of the most common and highly influential risk factors will give them the opportunity to reduce these risk factors and delay possible dementia onset.

In conclusion, non-demented older adults in this sample showed that (a) a combined risk score for genetic, demographic, health, and lifestyle factors was associated with EM performance and change, (b) select normal aging genetic polymorphisms (*COMT* and *BDNF*) show additive but not interactive synergistic influence on EF performance, and (c) *COMT* + *BDNF* additive synergistic effect is modified by *APOE* ε4+ allelic risk and further moderated by everyday lifestyle activities. This research establishes the need to examine specific synergistic associations

and combinations of select risk factors to understand the neurobiological mechanisms for neurocognitive performance in non-demented older adults.

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