Sex effects in predictors of memory resilience for carriers of Alzheimer's genetic risk

by

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Abstract

Apolipoprotein E (*APOE*) ε4 and Clusterin (*CLU*) C alleles are risk factors for Alzheimer's disease (AD) and preclinical cognitive and memory decline in older adults. We investigated whether memory resilience to genetic risk (i.e., Apolipoprotein E [*APOE*] ε4, Clusterin [*CLU*] CC, and a high additive genetic risk score [GRS]) is predicted by factors that are sex-specific and genetically robust. Using a longitudinal sample of cognitively normal adults (n = 642, aged 53-95) we defined memory resilience as possessing specified genetic risk while sustaining high episodic memory (EM) function over time. Random forest analysis, stratified by sex, tested the predictive importance of 22 risk factors derived from five documented AD risk domains: (a) demographic (e.g., education), (b) functional biomarker (e.g., pulse pressure), (c) health (e.g., diabetes), (d) mobility (e.g., walking time), and (e) lifestyle (e.g., everyday physical activity). For both sexes, younger age, higher education, stronger grip, and everyday novel cognitive activity predicted memory resilience. For females, demographic, functional, health, mobility, and lifestyle factors predicted resilience. For males, fewer depressive symptoms was an important predictor. Prediction patterns were similar for the two variants and the GRS. Long-term memory resilience in non-demented aging is predicted by risk and protective factors that are both common and unique to females and males. The greater number and wider breadth identified for females may enhance opportunities for sex-specific multi-factorial interventions to promote functional maintenance and delay cognitive decline. Promoting memory and cognitive resilience is especially crucial for aging adults with unmodifiable AD genetic risk.

Preface

This theses is an original work by Kirstie McDermott. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta, University of Victoria, and National Institutes of Health Research Ethics Boards.

A portion of this work is submitted for publication with co-authors G. Peggy McFall, Shea J. Andrews, Kaarin J. Anstey, and Roger A. Dixon. K. L. McDermott was responsible for concept formation, literature review, statistical analyses, and manuscript composition. G. P. McFall assisted with analyses and contributed to manuscript edits. S. J. Andrews assisted with analyses. K. J. Anstey contributed to manuscript edits. R. A. Dixon was the supervisory author and was involved with concept formation, manuscript composition, and edits.

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Table of Contents

List of Tables

List of Figures

Chapter 1 – Introduction

There is an urgent need to develop methods of promoting cognitive maintenance and functional capacity during aging (Jin, Simpkins, Ji, Leis, & Stambler, 2015). The emerging epidemic of AD and dementia in our rapidly aging society has prompted large-scale efforts to minimise their impact on individual well-being and their societal cost. At this time, secondary prevention of cognitive decline and dementia through individualized risk-reduction may be the optimal course of action (Anstey, Eramudugolla, Hosking, Lautenschlager, & Dixon, 2015; Bongaarts, 2009; Smetanin et al., 2009; Wortmann, 2012). To accomplish this task, a better understanding of the dramatic variations in neurobiological and neurocognitive aging processes is essential.

Older adults exhibit considerable heterogeneity in cognitive performance and trajectory. Although slight decline in ability is considered normal (Deary et al., 2009) and more rapid decline is evidence of preclinical disease, another empirically interesting subset of the population is able to maintain high levels of cognitive performance into late life (Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012; Yaffe et al., 2009). With the relatively new and emphasized endeavor to supplement post-diagnosis management with methods of delaying or preventing cognitive decline and dementia, research has also shifted from a focus on aging-related losses to include determinants of positive phenotypes (Martin et al., 2014). These recent initiatives include attention to protective or risk-reducing factors and mechanisms that may contribute to the attainment and maintenance of relatively healthy brain and cognitive aging (Depp, Harmell, & Vahia, 2012).

A wealth of evidence supports the independent and synergistic contribution of both non-modifiable (e.g., genetics, age) and modifiable (e.g., environment, lifestyle, health) factors to

interindividual differences in cognitive performance and dementia risk (Armstrong, Mitnitski, Launer, White, & Rockwood, 2013; de Frias & Dixon, 2014; McFall, Sapkota, McDermott, & Dixon, 2016; Thibeau, McFall, Wiebe, Anstey, & Dixon, 2016; Yaffe et al., 2009). In fact, a complex interaction between the genetic background and lifestyle-environmental influences of individuals can predict cognitive status and outcome, often independent of, or supplemented by, chronological age (DeCarlo, Tuokko, Williams, Dixon, & MacDonald, 2014; Rogalski et al., 2013). Given that some AD risk factors are non-modifiable, understanding which risk factors for cognitive decline are preventable and which protective factors for cognitive maintenance are attainable will enable us to develop strategies to preserve cognition and functional independence into late life, even in high-risk individuals. Such strategies may substantially decrease the prevalence of cognitive decline and dementia by delaying onset (Brookmeyer, Gray, & Kawas, 1998; Fratiglioni & Wang, 2007), or, more excitingly, preventing them altogether.

Despite carrying genetic risk for neurocognitive decline, some older adults maintain unexpectedly high levels of cognitive performance into late life (Kaup et al., 2015). The phenomenon of cognitive resilience may be influenced and predicted by other factors that contribute to risk reduction or brain and cognitive reserve and resilience. Therefore, although genetic risk is non-modifiable, other potentially modifiable factors exist that can attenuate, counteract, or protect against the accelerated risk of cognitive decline or impairment. For individuals with AD-related genetic risk, factors from demographic, cognitive, health, biological, and environmental-lifestyle domains play a role in determining cognitive trajectories and outcomes. Understanding how to predict or support cognitive resilience in at-risk older adults may enable researchers to identify specific, targetable mechanisms and pathways that influence these differential and variable patterns. Arguably, both delay and prevention of preclinical

cognitive decline, cognitive impairment, or dementia will be aided by a better understanding of the factors associated with healthy or resilient brain and cognitive aging (Anstey et al., 2014; Fotuhi, Hachinski, & Whitehouse, 2009).

The present thesis investigates a novel phenomenon: Memory resilience to AD genetic risk. We define resilience to two established and mechanistically similar AD genetic risk factors—the Apolipoprotein E (*APOE*) ε4 and Clusterin (*CLU*) C alleles. Because sporadic AD is a multi-factorial neurodegenerative condition and not all genetic risk carriers convert to clinical diagnosis or even to preclinical cognitive decline (Kaup et al., 2015), we reasoned that some genetic risk carriers would also maintain high levels of memory performance over time. We specifically investigated whether memory resilience to AD genetic risk is predicted by modifiable factors that are sex-specific and genetically robust. We used a large, longitudinal sample of cognitively normal older adults to examine three main research goals. First, we distinguished phenotypes of longitudinal memory performance to extract a relatively higher-performing memory aging group. This group was defined as having high levels of memory functioning that were sustained over time. Second, using a comprehensive set of 22 known AD risk and protective factors, we investigated sex differences in predictors of resilience in terms of (a) risk domain and specific factor and (b) relative importance. Third, we informally compared the generalizability of prediction patterns across both AD risk genes (*APOE* and *CLU*) and their combined genetic risk score (GRS).

Strategies to promote cognitive resilience in aging may arise following the examination of modifiable factors that can be assessed and targeted for intervention as early as mid-life. The present thesis focuses on 22 factors from five key AD risk and protective domains. We examine their importance in predicting resilience to memory decline in adults ranging from midlife to old

(53 – 95 years). The following literature review provides the relevant background material for this thesis, including: (a) an overview of resilient cognitive aging phenotypes, (b) brain and cognitive reserve, (c) episodic memory (EM), and (d) the unmodifiable (i.e., genetics, sex, age, education) and modifiable (i.e., demographics, functional biomarkers, health, mobility, and lifestyle) factors associated with cognitive and memory outcomes in aging adults.

Chapter 2 – Literature Review

2.1. Positive Phenotypes: Resilient Cognitive Aging

Across the globe, older adults are comprising a larger portion of the total population. Accordingly, there are greater numbers of age-related illnesses than ever before, including Alzheimer's disease (AD) as well as other causes of dementia and neurodegeneration. These cognitively devastating diseases severely diminish functional independence and societal contribution of both affected individuals and their caretakers. Even among non-demented adults, aging is associated with cognitive decline and impairment within most domains. These include episodic memory, processing speed, working memory, and executive function (Kirova, Bays, & Lagalwar, 2015; Park & Reuter-Lorenz, 2009). However, older adults exhibit vast interindividual variability in cognitive performance and trajectory (Small, Dixon, & McArdle, 2011; Wilson et al., 2002). In fact, some older adults experience little to no cognitive decline in aging (globally or within domains), suggesting that more severe impairment and decline is not necessarily an inevitable consequence of aging (Rowe & Kahn, 1987; Yaffe et al., 2009).

Interest in aging outcomes has thus shifted from a disease-centered focus to include complementary "positive biology" approaches that consider the neurobiology of healthy brain and cognitive aging. Specifically, this new focus seeks to identify protective factors, mechanisms, and neural correlates that contribute to an individual's ability to (a) attain and maintain healthy or successful cognitive phenotypes and (b) resist or be resilient to other risk factors that typically promote impairment and decline (Farrelly, 2012; Kaup et al., 2015; Martin et al., 2014; Rogalski et al., 2013; Rowe & Kahn, 1987; Yaffe et al., 2009; Yaffe et al., 2010). Thorough characterization of positive aging phenotypes may help us (a) develop interventions that promote cognitive and functional maintenance into late life and (b) delay, prevent, or treat

cognitive decline. Healthy cognitive aging phenotypes are associated with increased quality of life and decreased risk of death (Guehne, Luck, Busse, Angermeyer, & Riedel-Heller, 2007; Vance et al., 2008; Yaffe et al., 2010; Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006) and are distinguished by a number of characteristics. For example, above-average cognitive and memory aging phenotypes are associated with favorable demographic (e.g., higher literacy level), lifestyle (e.g., weekly exercise), health (e.g., no vascular disorders), genetic (i.e., *APOE* ε4-), cognitive (e.g., multi-domain advantages), brain (e.g., fewer markers of AD pathology), and clinical (i.e., lower levels of inflammatory markers) factors (de Frias, Dixon, & Strauss, 2009; Dixon & de Frias, 2014; Gefen et al., 2014; Harrison, Weintraub, Mesulam, & Rogalski, 2012; Josefsson et al., 2012; Rogalski et al., 2013; Yaffe et al., 2009).

Healthy brain and cognitive aging phenotypes also derive from another positive construct deemed "resilience". Resilient cognitive aging occurs when aging adults maintain relatively high levels of cognitive performance and functional independence into late life despite have a strong risk factor for impairment and decline. Researchers interested in cognitive resilience in aging adults typically investigate resilience to AD risk factors such as brain pathology. Those individuals identified as cognitively resilient often demonstrate an apparent discordance between AD-related pathology and cognitive performance and outcome (Negash et al., 2013a). More specifically, resilient older adults may exhibit substantial amyloid plaques, tau tangles, Lewy bodies, or vascular pathology yet maintain unexpectedly high levels of cognitive ability. Cognitive resilience to brain pathology is associated with a variety of favorable characteristics such as mid-life socioeconomic status, reading ability, genetics [e.g., *APOE*, *HS3ST3A1*], intracranial volume, cellular and synaptic features, and cognitive activity (Arnold et al., 2013; De Jager et al., 2013; Negash et al., 2013a; Negash et al., 2013b). Associating resilient phenotypes

with potentially modifiable factors from various domains (i.e., health, biomarkers, environmental) has promise for identifying (a) personalized ways to promote resilience or (b) mechanistic pathways for future intervention or treatment targets. Therefore, further examination of characteristics and pathways potentially involved in susceptibility or resilience to Alzheimer's risk factors is warranted.

Cognitive resilience to susceptibility genes for late-onset AD (namely the *APOE* ε4 allele) is another promising way to investigate factors that delay or prevent cognitive decline or dementia in the face of a strong, unmodifiable risk factor. Ferrari and colleagues (2011), with data from the Kungsholmen Project (individuals aged 75+ at baseline), investigated modifiable factors associated with reduced risk of AD and dementia in initially non-demented older adults with AD genetic risk. Their results indicated that carriers of the *APOE* ε4 allele with high education (i.e., ≥ 8 years), no vascular risk factors (i.e., high blood pressure, stroke, heart failure, diabetes, or prediabetes), and high participation in leisure activities (based on a combined score including participation in mental, social, and physical activities) had a reduced risk of dementia and AD as well as delayed time to onset (Ferrari et al., 2013).

A more recent study specifically investigated cognitive resilience to the *APOE* ε4 allele in a sample of 2487 cognitively normal older adult participants in the Health, Aging, and Body Composition study (69-80 years old at baseline; followed for up to 11 years). Kaup and colleagues (2015) defined participants as resilient if they had an above-average longitudinal global cognitive trajectory (i.e., were in the upper tertile based on Modified Mini-Mental State Examination performance trajectory) despite carrying the *APOE* ε4 allele (included ε2ε4, ε3ε4, and ε4ε4 genotypes). After stratifying their sample by race (i.e., black and white older adults), they tested predictors of cognitive resilience (versus non-resilience) to *APOE* ε4 allelic risk. In

both black and white older adults, resilience was predicted by demographic (i.e., literacy level of at least 9th grade, higher education) factors. Specifically for white older adults, resilience was also predicted by demographic (i.e., older age), psychosocial (i.e., no negative life events in the past year), and lifestyle (i.e., more time spent reading) factors. For black older adults, resilience was also predicted by demographic (i.e., female sex) and health (e.g., not being diabetic) factors. Their results support conclusions that (a) the phenomenon of cognitive resilience to AD genetic risk exists in non-demented aging adults and (b) numerous potentially modifiable factors predict resilience. However, their results also indicate that resilience is predicted differentially for nationally similar but demographically (i.e., racially) separate groups. Altogether, these two studies investigating cognitive resilience to AD genetic risk suggest that, although the *APOE* ε4 allele is a strong risk factor for cognitive decline and dementia, there are a number of modifiable psychosocial, environmental, demographic, health, and lifestyle factors that can promote resilience to the presumed negative neuropathological effects of AD genetic risk.

We developed a novel resilience classification of *memory resilience.* We define memory resilience as episodic memory (EM) performance that is relatively high and is maintained over time despite the presence of AD genetic risk. We specify two AD risk genes: *APOE* and *CLU* independently and in combination (i.e., an additive genetic risk score [GRS]). Our overall aim is to investigate whether memory resilience to multiple forms of AD genetic risk is predicted by modifiable, epidemiologically-indicated dementia risk factors. EM was evaluated over nine years based on performance on a latent variable composed of three indicators from two validated tasks. We examine three research goals. First, we aim to separate phenotypes of longitudinal memory performance to extract a relatively higher-performing memory aging group. Second, we investigate sex differences in predictors of resilience in terms of (a) risk domain and specific

factor and (b) relative importance. Third, we compare the generalizability of prediction profiles across *APOE*-, *CLU*-, and GRS-based resilience classification. We test the predictive importance of 22 factors: age, education, and 20 modifiable factors from demographic, functional biomarker, health, mobility, and lifestyle domains. We selected these domains and specific factors based on previous aging, resilience, epidemiological, and dementia research (Anstey et al., 2015; Ferrari et al., 2013; Josefsson et al., 2012; Kaup et al., 2015). The remainder of this literature review details the relevant background information specific to accomplishing the goals of this thesis.

2.2. Brain and Cognitive Reserve

External influences can promote or support cognitive resilience, potentially by enhancing reserve (Daffner, 2010), of which there are two main types. Brain reserve encompasses physical characteristics of the brain, such as volume and synaptic density, which enables it to withstand greater pathology (e.g., AD-related plaques and tangles) before a threshold is reached in which symptoms clinically manifest (Negash et al., 2013b; Sachdev & Valenzuela, 2009). Cognitive reserve arises from functional advantages such as network efficiency which also increase the threshold for pathological effects on cognition. Sufficient delay of cognitive decline and dementia through enhanced brain and cognitive reserve may decrease the number of diagnosed AD cases substantially (Brookmeyer et al., 1998; Fratiglioni & Wang, 2007). As such, there is much interest in identifying factors associated with brain and cognitive reserve.

Both forms of reserve independently and interactively contribute to resilience by (a) compensating for the loss and (b) buffering the pathology (Tucker & Stern, 2011; Valenzuela & Sachdev, 2006) imparted by identified risk factors, including AD risk alleles (Stern, 2012). In this thesis, we consider a number of risk and protective factors that may stimulate memory resilience to AD genetic risk factors by enhancing brain and cognitive reserve. Notably, reserve

can be promoted by lifestyle and environmental factors, including: (a) higher education, (b) occupational complexity, (c) socioeconomic status, (d) cognitively-stimulating lifestyle activities, (e) social activities, and (f) physical activities (Barulli & Stern, 2013; Fratiglioni & Wang, 2007). Reciprocally, lower reserve makes older adults more susceptible to the effects of risk factors (e.g., poor lifestyle), thereby negatively affecting global or specific (e.g., EM) cognitive performance. Based on our predictor analyses, we will contribute information about factors that promote resilience to AD genetic risk potentially by increasing brain and cognitive reserve.

2.3. Episodic Memory

EM is a declarative memory subtype broadly defined as the long-term memory for personal events situated in time and place. It allows for "mental time travel" to recall past personal experiences in detail and is imperative to shaping how we act and feel in each present moment (Tulving, 2002). EM generally declines with advancing age, but does exhibit differential aging changes among individuals and shows exacerbated decline in mild cognitive impairment (MCI) and AD (Dixon, Small, MacDonald, & McArdle, 2012; Jones, Harold, & Williams, 2010; Josefsson et al., 2012; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). Neuropathological outcomes of the aging process, including neuronal dysfunction and other brain pathologies (Nilsson, 2003), influence gradual EM decline in typically-aging adults (Dixon et al., 2004). Brain areas and neurotransmitters necessary for EM ability (e.g., the hippocampus and acetylcholine, respectively) are some of the first affected, and hardest hit, in preclinical cognitive decline and AD (Anand & Singh, 2013; Hasselmo, 2006; Nelson et al., 2012; Rugg & Vilberg, 2013). Correspondingly, a frequent complaint of older adults is diminished EM ability;

an abnormally pronounced deficit is one of the earliest signs of AD (Bäckman, Small, & Fratiglioni, 2001).

However, EM performance and change exhibits wide variation among individuals due to direct and indirect contributions of epidemiological risk and protective factors (Dixon et al., 2012). Accordingly, there is demonstrated potential for aging adults to have high (i.e., above average) and sustained EM performance trajectories, even into advanced age (Josefsson et al., 2012). Positive memory aging phenotypes are associated with a number of protective or risk-reducing factors (i.e., lifestyle engagement) that promote maintenance or contribute to reserve and resilience (Dixon et al., 2012; Nyberg et al., 2012). We aim to identify a relatively more adaptive or higher-performing memory aging phenotype in our sample based on each participant's longitudinal performance on an EM latent variable. We then define memory resilience as EM performance that is relatively high and is maintained over time despite the presence of AD genetic risk

2.4. Unmodifiable Risk Factors Influencing Cognition and Memory in Aging and AD

In this thesis, we considered four generally unmodifiable factors associated with AD risk, memory performance, and resilience. However, we assigned them different roles in this research. The first factor, AD genetic risk, defines our memory resilient groups. The second factor, sex, is used to stratify all our analyses in order to elucidate differences in predictors of resilience between females and males. The third and fourth factors, age and education, are used to define phenotypes of longitudinal EM performance and are also 2 of the 22 tested predictors of memory resilience (given their relevance and importance in resilient outcomes).

2.4.1. Genetics

Aside from age, genetic risk is the major non-modifiable risk factor for AD. Recently, there has been considerable interest, and success, in elucidating risk alleles for AD using genome-wide association studies (GWAS). As a result, several genetic single nucleotide polymorphisms (SNPs) have been identified as risk factors for sporadic AD. Interestingly, many of the risk SNPs identified also predispose normally-aging carriers to cognitive impairment or decline. Thus, researchers study risk alleles for AD in order to (a) understand the mechanisms behind AD and cognitive change and (b) predict transitions from normal aging to MCI or AD.

Several genetic polymorphisms have been robustly associated with increased risk of developing sporadic AD. Two such genes are *APOE* (rs429358 and rs7412; risk: ε4 allele) and *CLU* (*CLU*: rs11136000; risk: C allele). Both are associated with non-pathological and preclinical cognitive and memory decline in older adults (Schiepers et al., 2012; Thambisetty et al., 2013; Wu, Yu, Li, & Tan, 2012). Heritability estimates for EM are between 30% and 70% (Barral et al., 2013; Koppel & Goldberg, 2009). One study in particular indicated a heritability estimate of 62% in healthy older adults which remained unchanged after adjustment for number of *APOE* risk (ε4) alleles (Wilson et al., 2011). Studies investigating the association of novel genetic risk factors for cognitive decline and AD with neuropsychological performance have shown promise in elucidating potentially modifiable mechanisms of decline associated with genetic risk.

Apolipoprotein E

APOE is a gene located on chromosome 19 with three major isoforms: ε2, ε3, and ε4. It is implicated in many key brain health functions, including: (a) amyloid beta (Aβ) metabolism (e.g., aggregation and clearance), (b) neuroinflammation, (c) lipid transport, (d) glucose

metabolism, (e) neurogenesis and neuronal repair (e.g., of cholinergic neurons), (f) protection against oxidative stress, (g) synaptic plasticity, and (h) neuronal signaling (Bennet et al., 2007; Corder et al., 1993; Fotuhi et al., 2009; Liu, Kanekiyo, Xu, & Bu, 2013). The three isoforms differentially influence the listed functions—a notable example is their respective influence on Aβ deposition and clearance. Improper Aβ metabolism plays a major role in memory outcomes through direct (e.g., accumulation in memory brain areas) and indirect (e.g., synaptoxicity) pathways (Hudry et al., 2013; Lim et al., 2012; Lim et al., 2013b).

The *APOE* ε4 allele is the strongest known genetic risk factor for late-onset AD and is associated with both cognitive decline and MCI (Dixon et al., 2014; Liu et al., 2013; Schiepers et al., 2012). Each *APOE* ε4 allele increases AD risk by approximately four-fold and decreases age of onset (Brainerd, Reyna, Petersen, Smith, & Taub, 2011; Corder et al., 1993). Even healthy young (e.g., 20-39 year olds) carriers of the risk allele exhibit functional brain abnormalities (Reiman et al., 2004). The ε4 allele can predispose carriers to cognitive decline by acting alone (Schiepers et al., 2012) or in combination with other risk factors such as poor vascular health (Bangen et al., 2013), history of traumatic brain injury (Dardiotis et al., 2010), or other genes (Hayden, Lutz, Kuchibhatla, Germain, & Plassman, 2015). Conversely, the ε2 allele is considered non-risk or, more often, protective, as carriers exhibit reduced risk of cognitive decline and AD (Suri, Heise, Trachtenberg, & Mackay, 2013) and better cognitive performance (Small, Rosnick, Fratiglioni, & Backman, 2004). The most common ε3 allele is generally considered neutral or non-risk (Corbo & Scacchi, 1999).

Research examining the relationship between *APOE* and EM has indicated that typically aging carriers of at least one ε4 allele exhibit worse EM performance and steeper decline (Lim et al., 2015; McFall et al., 2015; Schiepers et al., 2012; Small et al., 2004). Specifically, EM may

be negatively affected in ε4 carriers through (a) reduced functional connectivity in brain areas associated with EM (Chen, Shu, Wang, Liu, & Zhang, 2016), (b) hippocampal atrophy (Kerchner et al., 2014), (c) abnormal cell turnover (Wikgren et al., 2012), and (d) AD pathology (i.e., plaques and tangles) (Lim et al., 2015; Yu, Boyle, Leurgans, Schneider, & Bennett, 2014). Some controversy about this relationship still exists as some studies have failed to find evidence of an association between the ε4 allele and EM performance (Raz, Rodrigue, Kennedy, & Land, 2009). However, because the ε4 allele is an established AD risk allele, we define normally-aging *APOE* ε4 carriers with little-to-no EM decline over nine years as memory resilient to *APOE* risk and investigate modifiable predictors of this novel phenotype.

Clusterin

A related genetic risk factor in a SNP within the *CLU* gene, located on chromosome 8, is also significantly associated with AD as demonstrated by recent GWAS (Carrasquillo et al., 2010; Harold et al., 2009; Wijsman et al., 2011). On average, it increases the risk of AD by approximately 10-15% (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007; Harold et al., 2009). Apolipoprotein J (ApoJ)—the protein encoded by *CLU*—is involved in brain-related functions such as: (a) Aβ metabolism and pathophysiology (Desikan et al., 2014), (b) lipid regulation and transport (Baralla et al., 2015), (c) oxidative stress (Trougakos, 2013), and (d) inflammation (Falgarone & Chiocchia, 2009). The *CLU* rs11136000 SNP has two alleles—C and T. The major C allele increases AD risk whereas the T allele is considered non-risk (Bertram et al., 2007).

GWAS have implicated the *CLU* C allele in poorer cognitive and EM performance and decline (Sweet et al., 2012), even after ruling out effects of the *APOE* ε4 allele. The C allele is associated with steeper memory decline in cognitively normal, pre-symptomatic individuals who

later progress to MCI (Thambisetty et al., 2013). The risk allele may negatively affect EM by influencing: (a) white matter integrity (Bertram & Tanzi, 2010; Braskie et al., 2011; Lockhart et al., 2012), (b) functional connectivity between memory brain regions (e.g., coupling between the hippocampus and dorsolateral prefrontal cortex) during EM retrieval (Erk et al., 2011), (c) brain activity during demanding memory tasks (Lancaster et al., 2011), (d) hippocampal blood flow (Thambisetty et al., 2013), and (e) ventricular expansion (Roussotte, Gutman, Madsen, Colby, & Thompson, 2014). Even healthy young individuals with the CC genotype exhibit hyperactivation in memory brain areas (Lancaster et al., 2011; Lancaster et al., 2015). In contrast, the AD non-risk *CLU* T allele was associated with better general cognitive performance (in a sample of individuals 90 years or older) on a composite consisting of EM, working memory, and verbal fluency tasks (Mengel-From, Christensen, McGue, & Christiansen, 2011). *CLU* TT homozygotes are also protected from the negative cognitive effects attributed to worse personality phenotypes (i.e., high neuroticism) (Sapkota, Wiebe, Small, & Dixon, 2015). As with *APOE*, we define normally-aging adults with a high-risk (i.e., CC) *CLU* genotype and little-to-no EM decline as memory resilient to *CLU* risk and investigate predictors of the phenotype. Because the *CLU* C allele imparts lower relative risk for AD than the *APOE* ε4 allele (Adams et al., 2015; Bertram et al., 2007), we defined memory resilience to the CC genotype as opposed to just C allele carriers (i.e., CC or CT genotype).

Apolipoprotein E and Clusterin

We chose to investigate memory resilience to these two genes specifically due to their mechanistic similarities, functional relationship, cooperative roles (e.g., Aβ metabolism), and potential to influence EM in normal aging. For example, McFall and colleagues (2016) recently found that both the *APOE* and *CLU* non-risk alleles and their combined GRS attenuated the

negative effect of poor vascular health on executive function performance and decline. In another study, these risk alleles were associated (independently and in combination) with entorhinal cortex volume in young adults (DiBattista, Stevens, Rebeck, & Green, 2014). Therefore, this thesis will additionally consider memory resilience to an additive *APOE* and *CLU* GRS.

We briefly discuss the rationale for including a GRS component in this paper. The multifunctional proteins encoded by *APOE* and *CLU* (Apolipoprotein E [ApoE] and ApoJ, respectively) are related and involved in maintaining healthy brain function (Elliott, Weickert, & Garner, 2010). The molecules share some common functions, including: (a) cholesterol and lipid transport and metabolism (Elliott et al., 2010), (b) Aβ metabolism and clearance (DeMattos et al., 2004), (c) binding to common receptors (Leeb, Eresheim, & Nimpf, 2014), (d) promotion of neuronal growth, (e) synapse turnover (Bertram & Tanzi, 2010), and (e) brain structure, even in young adults (Braskie et al., 2011; DiBattista et al., 2014). Although still under investigation, ApoJ may interact with ApoE to provide supplemental neuroprotection and process Aβ (i.e., moderate its uptake, clearance, solubility, degradation, and transport) (Holtzman, 2004). Taken together, the risk alleles of *APOE* and *CLU* may influence cognitive decline through increased AD pathology and neuronal loss (Elliott et al., 2010; Morris et al., 2010; Roussotte et al., 2014). The additional risk imparted by having a high additive GRS may be reflected by a slightly differential pattern of predictors of memory resilience. However, we expect similar patterns of predictions to those obtained by testing resilience to the risk genes independently.

2.4.2. Sex

Males and females have many important biological and behavioural differences which contribute to dissimilarities in cognition, aging trajectory, and risk of disease. Although the terms sex and gender are often used interchangeably, in this study we specifically use the term sex to

underscore the biological nature of this research. Briefly, sex is generally considered innate and biological whereas gender arises from psychosocial and cultural factors (Johnson & Repta, 2012). As such, sex- and gender-derived factors or differences influence cognitive outcomes in aging from slightly different perspectives (e.g., hormones and brain structure versus accessibility to education and caregiver roles, respectively) (Mielke, Vemuri, & Rocca, 2014). In this study, we target a large number of biologically-focused factors and their potential effect on systems and mechanisms within the brain and body which can contribute to differences in cognition and memory, health and physiology, and dementia prevalence (Li & Singh, 2014). However, characteristics associated with both sex and gender likely influence the processes and outcomes we investigated. For example, whereas grip strength and statin use may be more sex-related, marital status and level of social activity may reflect gender influences.

Specific to cognition and cognition-related outcomes, aging males demonstrate steeper decline in performance on tests from numerous cognitive domains (McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016) and are at a higher risk of MCI (Roberts et al., 2012). As such, females may be less vulnerable (or more resilient) to the neuropathological effects of aging on cognition (McCarrey et al., 2016). However, females are disproportionally more likely to develop AD (Li & Singh, 2014; Thies & Bleiler, 2013) because of neurobiological mechanisms that are beginning to be understood. Manifestations of these mechanisms include earlier onset of pathogenic brain changes and steeper trajectories of decline (Zhao, Mao, Woody, & Brinton, 2016). Furthermore, although the *APOE* ε4 allele increases risk of conversion to MCI and AD in both females and males, the effect is stronger in women, possibly because of differing levels of brain pathology (Altmann, Tian, Henderson, & Greicius, 2014).

There are also established sex differences in EM performance and change which vary by task (Nilsson, 2003). Across the lifespan, females generally outperform males on verbal and word list tasks. In contrast, males outperform females on EM tasks with a visuospatial component (de Frias, Nilsson, & Herlitz, 2006; Herlitz & Rehnman, 2008). Notably, aging females also have a greater likelihood of following above-average (i.e., successful) EM trajectories (Josefsson et al., 2012). To investigate longitudinal EM performance in this study, we used three indicators from two EM tasks (Word Recall and Rey Auditory Verbal Learning [RAVLT]) to create a latent EM variable. On average, females outperform males on both these EM tasks (Herlitz & Rehnman, 2008; Jack et al., 2015) further emphasizing the importance of our decision to include sex-stratification. As with general cognition, a variety of factors from lifestyle, environmental, health, and biological domains can further affect the magnitude of sex differences in EM. For instance, sex-specific differences in EM may arise as a result of divergent (a) brain structure and function, such as memory retrieval strategies (Young, Bellgowan, Bodurka, & Drevets, 2013), (b) stress response (Guenzel, Wolf, & Schwabe, 2014), (c) hormones (Li & Singh, 2014), and (d) lifestyle (e.g., cognitive and physical activity, education and occupation, and smoking habits) (Mielke et al., 2014).

Given that sex strongly influences cognitive performance and risk of disease (Li & Singh, 2014), many cognitive aging studies are now stratifying by sex as part of their research prerogative (Kok, Aartsen, Deeg, & Huisman, 2015). One major aspect of this study will be to examine sex differences (and similarities) in predictors of memory resilience to AD genetic risk. Given observed sex differences in risk and performance, patterns of predictors of memory resilience to the *APOE* and *CLU* risk alleles may also vary by sex. Examining sex differences in memory resilience to AD genetic risk may have implications for interventions to reduce risk of

functional disability and neurodegenerative disease. A better understanding of sex differences (and their biological basis) will provide insight into specific or targeted risk factors that contribute to normal and pathological cognitive impairment and decline (Li & Singh, 2014). Although sex-specificity is still not in the mainstream of cognitive aging, impairment, and AD research, we emphasize the need for such considerations in standard research, mechanistic interpretation, interventions, clinical trials, preventions, and treatments.

2.4.3. Age

Age is the single greatest risk factor for sporadic AD (Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000) and incidence of AD spikes after age 65 (Alzheimer's Association, 2016). The brains of non-demented aging adults often display AD-like pathology, including regions of Aβ accumulation and cortical volume loss (Chetelat & Fouquet, 2013). As such, older age is also a strong, unmodifiable risk factor for cognitive decline across multiple domains, including memory (Lipnicki et al., 2013), in normally-aging adults. However, the effect of age on cognitive function can be reduced in the presence of protective factors from multiple domains (e.g., health, physiological, and psychosocial) (Hendrie et al., 2006). In this study, we used age as one of our 22 predictors of memory resilience to AD genetic risk. Although our focus was on potentially modifiable factors, we included age to (a) control for its strong effect on EM outcome and (b) assess its relative importance (with respect to the other, modifiable factors) in predicting resilience.

2.4.4. Education

Low education is a risk factor for cognitive impairment, decline, and AD (Bennett et al., 2003; Caamano-Isorna, Corral, Montes-Martinez, & Takkouche, 2006). Accordingly, higher levels of education are generally associated with favorable outcomes (Britton, Shipley, Singh-

Manoux, & Marmot, 2008), including better cognition (Le Carret, Lafont, Mayo, & Fabrigoule, 2003) and lower risk of dementia. Higher levels of education may exert benefit by increasing cognitive reserve (Le Carret et al., 2003). Further evidence for the reserve theory comes from AD patients. Those AD patients with higher education exhibit greater brain pathology and dysfunction at diagnosis (e.g., more severe reduction in brain glucose metabolism) (Garibotto et al., 2008) and steeper cognitive decline in early disease stages (Andel, Vigen, Mack, Clark, & Gatz, 2006). One possible reason is that the pathological effects on function and cognition are buffered by reserve and appear later (Hall et al., 2007). However, results from studies investigating the association between educational attainment and cognition in aging are mixed. For example, one study found that education did not have an effect on cognitive change over six years (Van Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008). Some studies instead suggest that education is associated with passive cognitive reserve such that individuals with higher levels of education have better cognitive performance but decline at the same rate as their less-educated peers (Zahodne et al., 2011).

In this study, we consider level of education to be an unmodifiable risk (or protective) factor for EM performance and change. However, we note that there is evidence that education late in life (e.g., between 50 – 79 years of age) can increase cognitive reserve, offering another potential strategy to improve cognitive function or delay decline (Lenehan et al., 2015). Regardless, we proceed with the assumption that the vast majority of adults 53 years of age and older (as represented in our sample) will participate in further education or training at a level negligible to the current study. Moreover, those who do participate in further educational activities would likely benefit only marginally. Like age, we (a) account for the effect of education on EM and predictors of resilience by including it as a covariate in all our statistical

models and (b) test its relative importance as a predictor of resilience compared to the other (modifiable) factors.

2.5. Modifiable Factors from Five Domains of AD Risk and Protection

A wealth of potentially modifiable factors affect cognition and memory in aging. A number of lifestyle choices, environmental influences, health characteristics, and demographic factors act independently or interactively to affect cognition and risk of AD (Anstey et al., 2014). This section will discuss the 20 modifiable factors within five major domains of AD risk and protection (i.e., demographic, functional biomarker, health, mobility, and lifestyle) that we investigated as possible predictors of memory resilience. We emphasize that, in total, we test 22 factors as predictors of resilience: age, education, and the following 20 modifiable factors.

2.5.1. Demographic Factors

Some potentially modifiable demographic characteristics that may affect memory resilience include marital status, living with someone, and owning a pet. Previous studies have found that living with someone (including through marriage) is associated with successful cognitive and memory aging (Josefsson et al., 2012; Yaffe et al., 2009). Marriage and living with someone may provide social support and prevent isolation which protect against cognitive decline and dementia (i.e., provide resilience) by enhancing cognitive reserve, promoting a healthier lifestyle, providing widespread brain stimulation, and reducing stress (Pillai & Verghese, 2009). Older adult participants (aged 65+), particularly men, in the Swedish National Study on Aging and Care-Kungsholmen projects that reported living alone were at a higher risk of institutionalization and mortality than those who lived with at least one other person (Pimouguet et al., 2015). For older adults who are not able to live with a spouse or other human, pet ownership may provide some of the benefits of cohabitation by encouraging participation in

beneficial lifestyle activities (e.g., physical, cognitive, and social) and reducing stress (Cherniack & Cherniack, 2014). Given that being married and living with someone have widespread beneficial effects, we expect that both factors will emerge as important predictors of memory resilience.

2.5.2. Functional Biomarkers

Functional biomarkers are measures of physiological functioning, such as cardiovascular health (blood pressure, lung capacity, heart rate) and strength (sarcopenia, grip strength). Biomarkers representing these functions decline with typical aging and can be indicative or predictive of cognitive decline, impairment, and AD (DeCarlo et al., 2014; Dolcos, MacDonald, Braslavsky, Camicioli, & Dixon, 2012). Based on previous neuroepidemiological and cognitive aging literature, we focused on four main functional biomarkers available in our dataset: (a) pulse pressure (PP), (b) grip strength (GS), (c) peak expiratory flow (PEF), and (d) body mass index (BMI).

PP (systolic blood pressure minus diastolic blood pressure) is a representation of arterial stiffness whereby higher values indicate decreased vascular health (Raz, Dahle, Rodrigue, Kennedy, & Land, 2011; Steppan, Barodka, Berkowitz, & Nyhan, 2011). It is considered a better predictor of vascular health than systolic or diastolic blood pressure alone (Raz et al., 2011). Higher levels of PP are associated with poorer cognition (including executive function and EM) and increased risk of AD (Al Hazzouri & Yaffe, 2014; McFall et al., 2015; Qiu, Winblad, Viitanen, & Fratiglioni, 2003; Raz et al., 2011). Researchers with the Victoria Longitudinal Study (VLS) found that higher PP increases the risk of EM decrements in aging *APOE* e4 carriers (McFall et al., 2015). In the Baltimore Longitudinal Study of Aging, higher PP was associated with declines across multiple cognitive tasks including global cognition, verbal

learning, working memory, and nonverbal memory (Waldstein et al., 2008). Conversely, better cardiovascular health (i.e., lack of hypertension) has been associated with successful cognitive aging (Yaffe et al., 2009).

GS is reliably associated with clinical and cognitive outcomes. Assessing GS is the recommended way to measure sarcopenia (loss of muscle tissue) in older adults (Lauretani et al., 2003). Both GS and sarcopenia have been studied as markers of aging transitions—GS declines and sarcopenia increases with aging, respectively—and cognitive change (Lauretani et al., 2003; MacDonald, DeCarlo, & Dixon, 2011; MacDonald, Dixon, Cohen, & Hazlitt, 2004). Maintained muscle strength is associated with slowed rates of cognitive decline and decreased risk of MCI and AD (Boyle, Buchman, Wilson, Leurgans, & Bennett, 2009). In a cross-sectional cohort of healthy older male veterans (aged 65+) sarcopenia was related to both cognitive impairment and, interestingly, depressive symptoms (Hsu et al., 2014). A similar, longitudinal result was found in older females: Change in global cognition was associated with grip strength (as well as chair stands) (Atkinson et al., 2010).

PEF, a measure of lung function, is linked to maintenance of cognitive function or cognitive decline (Cook et al., 1995; MacDonald, DeCarlo, & Dixon, 2011; Rowe & Khan, 1997). Very impaired PEF in older adults is a strong predictor of incident AD (Simons, Simons, McCallum, & Friedlander, 2006) but respiratory function as early as in midlife is associated with an individual's risk of developing AD (Guo et al., 2007). A physical fitness indicator variable composed of expiratory volume, grip strength, and walking time was associated with cognition in older adult participants in the Lothian Birth Cohort 1921 (Deary, Whalley, Batty, & Starr, 2006). Remarkably, respiratory training may have the potential to improve cognitive function in older adults (Ferreira, Tanaka, Santos-Galduróz, & Galduróz, 2015).

Obesity (generally defined as BMI ≥ 25) at midlife increases the risk of dementia. However, there is some evidence of age effects such that, in older adults, low BMI may be a greater risk factor for dementia. Nevertheless, Barnes and Yaffe (2011) suggest that a 10-25% reduction in obesity rates could substantially decrease the prevalence of AD (Barnes & Yaffe, 2011). Obesity can negatively affect cognition in midlife and during normal aging, possibly through influences on ischemic white matter damage and general brain atrophy (Gustafson, Steen, & Skoog, 2004; Ward, Carlsson, Trivedi, Sager, & Johnson, 2005). Notably, older adults that maintained high levels of global cognition had lower BMI (Yaffe et al., 2009).

Altogether, these four biomarkers represent a range of functional health and related factors related to brain health and memory resilience in aging. Each of the four biomarkers may be related to (a) levels of brain and cognitive reserve, (b) frailty, (c) overall physiological health, or (d) brain and vascular pathology. As such, we expect that favorable levels of each factor will emerge as important predictors of resilience, perhaps differentially by sex.

2.5.3. Health Characteristics

Although a wealth of health characteristics influence cognitive aging and may affect memory resilience, we have selected six health characteristics available in the VLS that were also investigated in other successful and resilient cognitive aging studies (Ferrari et al., 2013; Josefsson et al., 2012; Kaup et al., 2015; Yaffe et al., 2009). Specifically, we tested: (a) subjective health, (b), depressive symptoms, (c) diabetes, (d) anti-inflammatory medication, (e) statin use, and (f) history of head injury.

Older adults following successful or resilient cognitive aging trajectories with a healthy profile within other domains may be aware of their more favorable aging outcome. For example, adults that rate their subjective health as “good” or better are more likely to maintain global

cognitive function over time (Yaffe et al., 2009), but only in some studies (Yaffe et al., 2010). We will determine whether this effect exists for memory resilient female and male older adults.

Non-clinical depressive symptoms may be a preventable risk factor for cognitive impairment and dementia (Wang & Blazer, 2015). In normal aging, elevated depressive symptoms are associated with lower memory performance and steeper decline (Lohman et al., 2013). Furthermore, older adults with relatively high levels of depressive symptoms (i.e., with scores in the upper tertile) are at a 50% higher risk of dementia (Simons et al., 2006). Therefore, we expect that lower depressive symptoms will be predictive of memory resilience.

Type 2 diabetes is an established risk factor for cognitive dysfunction and AD or other forms of dementia (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006; Yeung, Fischer, & Dixon, 2009). Dysregulated brain insulin can contribute to AD-related pathology thereby affecting cognition (Roriz-Filho et al., 2009; Umegaki, 2014). Older adults with diabetes symptoms have specifically demonstrated EM deficits, including impairment (Dahle, Jacobs, & Raz, 2009) and faster rates of decline (Okereke et al., 2009). Not being diabetic was an important predictor of cognitive resilience in black (but not white) older adults (Kaup et al., 2015). Because our sample is primarily composed of Caucasian Canadians, we suspect that memory resilience may not be predicted by diabetes status. However, our sex-stratified sample may yield different results than those obtained by Kaup and colleagues (2015).

Inflammation and cholesterol levels were recently investigated as predictors of cognitive resilience to the *APOE* ε4 allele (Kaup et al., 2015). Although we did not collect data on blood markers of inflammation and cholesterol, we reasoned that taking anti-inflammatory and cholesterol medication (i.e., statins) could act as proxy measures. Both inflammation and high cholesterol have been associated with exacerbated age-related cognitive decline (Lim, Krajina, &

Marsland, 2013a; van Vliet, 2012) and increased risk of dementia (Engelhart et al., 2004; Mainous, Eschenbach, Wells, Everett, & Gill, 2005). Of note, ApoE and ApoJ are involved in lipid function. However, it is possible that statin use may actually decrease the risk of cognitive decline or dementia (Cramer, Haan, Galea, Langa, & Kalbfleisch, 2008).

Self-reported history of head injury (e.g., concussion) is associated with increased risk, and earlier onset, of MCI and AD (Abner et al., 2014; LoBue, Lacritz, Hart, Kyle, & Cullum, 2014). The brains of individuals that have experienced a traumatic brain injury show accelerated brain atrophy and appear "older", which can affect cognitive and memory outcome (Cole, Leech, & Sharp, 2015). Given the long-term cognitive risk associated with head injuries, we expect that not having history of a head injury will emerge as a predictor of memory resilience.

2.5.4. Mobility

We investigate two principal indicators of mobility: walking time (i.e., gait) and turning time (i.e., balance). A recent review suggests that aging adults who maintain a high combined level of fitness and mobility are protected from aging effects on the brain, including areas involved in memory, which slows cognitive decline (Zhao, Tranovich, & Wright, 2014). Accordingly, cognition and mobility are related (Buchman, Boyle, Leurgans, Barnes, & Bennett, 2011) such that reduced mobility is associated with cognitive impairment, including MCI (Sachdev et al., 2012) and dementia (Abellan van Kan et al., 2012). Given the relationship between physical health, mobility, and cognitive performance (Mielke et al., 2013), it is possible that maintaining higher levels of both mobility factors may (a) promote memory resilience directly or (b) be a marker for a level of physical health associated with resilience through enhanced brain reserve.

2.5.5. Lifestyle

There is a general consensus that a healthy lifestyle (e.g., participation in physical, social, and cognitive activities) is beneficial to present and future cognitive ability (Hughes, 2008). Participation in lifestyle activities may promote healthy brain and memory aging by building brain and cognitive reserve, improving cardiovascular health, or reducing stress (Anstey et al., 2014; Dolcos et al., 2012; Small, Dixon, McArdle, & Grimm, 2012). More specifically, lifestyle-related boosts in brain and cognitive reserve can emerge as a result of increases in neurotropic factors, neurogenesis, and enhanced functional connectivity and flexibility of neural networks and processes (Hertzog, Kramer, Wilson, & Lindenberger, 2008; Kempermann, Gast, & Gage, 2002). Increasing participation in cognitive, physical, and social lifestyle activities is one of the easiest interventions strategies to implement in early-, mid-, and late-life to promote cognitive maintenance and resilience.

Frequent engagement in physically-, socially-, and cognitively-stimulating lifestyle activities is associated with better cognitive and memory performance and trajectory (Fratiglioni & Wang, 2007; Kramer, Erickson, & Colcombe, 2006; Lachman, Agrigoroaei, Murphy, & Tun, 2010; Nouchi et al., 2014; Scarmeas & Stern, 2003). We broadly considered physical and cognitive activity based on self-reported participation in 4 and 27 activities, respectively. For social activity, we specifically measured frequency of social visits and volunteering to replicate what was done by Kaup and colleagues (2015). Given that high participation in all social, cognitive, and mental activities predicted resilience in a previous study (Ferrari et al., 2013), we expect that each of the four activities will predict memory resilience, although perhaps differentially by sex.

We consider two additional lifestyle-related AD risk factors: consumption of alcoholic beverages and tobacco use. We note that neither smoking nor alcohol consumption were important predictors of cognitive resilience to the *APOE* ε4 allele, suggesting their overall effect, at least when other factors are considered, may be negligible (Kaup et al., 2015). However, both smoking and moderate alcohol consumption have documented risk and protective effects, respectively, for AD and dementia and are often used in risk indices (Anstey et al., 2014; Simons et al., 2006). Even in normal aging, older adults whose performance on a test of global cognition does not decline over time are more likely to have moderate alcohol intake and to be non-smokers (Barnes et al., 2007; Yaffe et al., 2009). Unfortunately, smoking status could not be included in any of our prediction models due to low prevalence of smokers when we parsed participants into groups by sex and genetic risk.

2.6. The Present Study

This study examined whether memory resilience to AD genetic risk is predicted by factors that may differ by sex but are similar across three genetic risk indicators (i.e., the *APOE* ε4 allele, the *CLU* CC genotype, and a high additive GRS). We had three research goals. First, we differentiated female and male participants as memory resilient or non-resilient to AD genetic risk based on nine-year longitudinal EM latent variable trajectory. This goal was accomplished using group-based trajectory (i.e., growth mixture) modelling to determine phenotypes of EM performance over nine years (Pietrzak et al., 2015). Second, we investigated sex differences in predictors of resilience in terms of (a) risk domain and specific factor and (b) relative importance using random forest analysis (RFA). Although still novel in its application to biomedical and neuroscience research, we specifically chose RFA because it is a nonparametric technique that can deal with large numbers of (potentially correlated) predictor variables even with relatively

small sample sizes (Strobl, Malley, & Tutz, 2009). We identified a pool of predictors derived from demographic, functional, health, mobility, and lifestyle domains based on previous brain and cognitive aging research (Anstey et al., 2015; Josefsson et al., 2012) and two studies that investigated general cognitive resilience associated with the *APOE* ε4 allele (Ferrari et al., 2013; Kaup et al., 2015). Third, we informally (a) compared the generalizability of prediction patterns across *APOE*- and *CLU*-based resilience classification and (b) assessed the overlap between genetically robust predictors and GRS-based resilience predictors.

We expected our trajectory analyses would reveal two or three distinguishable memory trajectory phenotypes from which "high-performers" and "low-performers" could be appropriately differentiated (Pietrzak et al., 2015; Terrera, Brayne, & Matthews, 2010; Zahodne et al., 2015). Based on previous findings, we hypothesized resilience prediction patterns would comprise a number of risk-reduction or protective factors. We expected the profiles would represent a range of domains, including demographic (e.g., marital status), functional biomarker (e.g., grip strength), health (e.g., subjective health), mobility (e.g., walking time), and lifestyle (e.g., physical activity) domains (Ferrari et al., 2013; Kaup et al., 2015). Because different cognitive domains and trajectories may respond differently to environmental and lifestyle factors (Kramer, Bherer, Colcombe, Dong, & Greenough, 2004), we suspected we would find interesting similarities and differences in predictors to those obtained by Kaup and colleagues (2015). We further hypothesized that some factors predictive of resilience to AD genetic risk would emerge as sex-similar whereas other would be sex-specific. Finally, we expected generalizability of any sex-specific differences across *APOE, CLU*, and GRS risk given their mechanistic similarities.

There is currently much demand for the identification of (a) risk factors for preclinical cognitive decline and (b) protective factors that can promote sustained, high levels of cognition into late life. Different cognitive aging trajectories reflect varying contributions of combined behavioural, environmental-lifestyle, demographic, and genetic factors. Research is shifting to include a focus on uncovering modifiable, non-pharmaceutic influences on cognitive aging outcome to develop disease prevention strategies. Our research aims to contribute to the discovery of potential risk-reduction targets that could conceivably increase or maintain the quality of life of older adults and, in turn, decrease the societal and economic burden of our aging population.

Chapter 3 – Method

3.1. Participants

Participants were community-dwelling older adult volunteers of the Victoria Longitudinal Study (VLS), an ongoing, multi-cohort, longitudinal-sequential study of genetic, health, cognitive, biomedical, and neuropsychological aspects of human aging. Participants were enrolled through community advertisements and received a small honorarium. All participants provide written informed consent and all data collection procedures are in full compliance with human research ethics. Further information regarding participant recruitment and longitudinal procedures can be found elsewhere (Dixon & de Frias, 2004).

We assembled archived longitudinal data from three VLS samples. Participants in each sample were initially recruited during a different decade (i.e., 1980s, 1990s, 2000s), reflecting the longitudinal-sequential nature of these data. At intake, participants were aged 53-85 and then were followed at regular intervals. Specifically, we obtained data from: (a) Sample 1 Wave 6 and 7, (b) Sample 2 Waves 4 and 5, and (c) Sample 3 Waves 1, 2, and 3. The respective earliest wave of each sample became Wave 1 (W1 or baseline, consisting of Sample 1 Wave 6, Sample 2 Wave 4, and Sample 3 Wave1), the second wave became Wave 2 (W2, consisting of Sample 1 Wave 7, Sample 2 Wave 5, and Sample 3 Wave 2) and the third wave became Wave 3 (W3, consisting only of Sample 3 Wave 3). The mean interval between the waves of data collection was 4.5 years (W1-W2; W2-W3).

A subset of the VLS database was used for this study. Specifically, we targeted genotyped participants. The VLS genotyping occurred in the 2009-2011 period and was limited by funding arrangement to approximately 700 continuing VLS participants in Samples 1 - 3. This VLS genetic cohort (n = 695; 67.2% female; mean age = 70.6 years; age range, 53 – 95

years) has accumulated up to three waves (nine years) of data. With these data, an accelerated longitudinal design covers a 40-year band of aging. We applied the following exclusionary criteria to the source sample: (a) EM data missing from all three waves (n = 45), (b) diagnosis of AD or dementia (n = 0), (c) self-report of "severe" for potentially comorbid conditions (i.e., epilepsy, head injury, encephalitis) (n = 7), and (e) self-report of "moderate" or "severe" for comorbid disease (i.e., Parkinson's disease) (n = 1). As with previous research (Kaup et al., 2015), our limited exclusionary criteria allowed us to maintain a reasonably diverse study sample that was fully genotyped.

Participant demographic and retention data for our study sample are presented in Table 3.1. N = 642 participants were available at Wave 1 (426 [66.4%] female and 216 [33.6%] male; mean age = 70.7 years; age range, 53 – 95). At Wave 2 we had 529 participants (349 female and 180 male) and at Wave 3 we had 304 participants (207 female and 97 male). Like prior VLS research (McFall et al., 2015), the subsample wave-to-wave retention rates ranged from 78% to 91% (Table 3.1). In this study, the longitudinal design was used only to develop memory trajectories for resilience classification.

3.2. DNA Extraction and Genotyping

Using the manufacturers' protocol, we obtained genetic markers from saliva samples that were collected according to Oragene DNA Genotek technology and stored at room temperature. DNA was manually extracted from 0.8 ml of saliva sample mix. Genotyping was carried out by using a polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) strategy to analyze allele status for *APOE* (determined by the combination of the single nucleotide polymorphisms [SNPs] rs429358 and rs7412) and *CLU* (rs11136000). Briefly, SNP-containing PCR fragments were amplified from 25ng of genomic DNA using primers for *APOE*

(Forward: 5'-GGCACGGCTGTCCAAGGA-3', Reverse: 5'-GCCCCGGCCTGGTACACTGCC-3') and *CLU* (Forward: 5'-AAAGCAGGCTGCAGACTCC-3', Reverse: 5'-AGTGCTGGGATTACAGGTGTC-3'). PCRs were completed in the QIAgility robotic system (QIAgen). RFLP was performed on a high-resolution DNA screening cartridge on a QIAxcel capillary electrophoresis system using the protocol OL700 after digestion of the PCR amplicons. Restriction enzymes (from NE Biolabs) included (a) HhaI (16 hours at 37°C) for *APOE* and (b) Tsp509I (4 hours at 65°C) for *CLU*. Migration of the restriction fragments on 10% or 15% of acrylamide gels for each SNP confirmed the analyses.

As mentioned, *APOE* genotype was determined by the combination of SNPs rs429358 and rs7412. The *APOE* ε4- genotype consisted of ε2ε2, ε2ε3, and ε3ε3 (n = 463) and the ε4+ genotype consisted of ε2ε4, ε3ε4, and ε4ε4 (n = 179). There were three potential *CLU* genotypes: TT (n = 105), TC (n = 320), and CC (n = 216). One participant only contributed an *APOE* genotype due to an error during *CLU* extraction. Results of Hardy-Weinberg equilibrium analyses showed that the allele frequency distributions of both *APOE* (clustered according to the presence of the risk ε4 genotype; $\chi^2 = 0.47$, $p = 0.492$) and *CLU* ($\chi^2 = 0.55$, $p = 0.458$) were within population norms (Table 3.2). Our sample consisted of mainly Caucasian Canadians, and the allelic frequencies were comparable to those of previous studies with participants of similar demography (Barral et al., 2012; Deary et al., 2004; Ferencz et al., 2014)

Resilience to *APOE* genetic risk required carrying at least one *APOE* ε4 allele. Given the disparity in odds ratios between *CLU* (C = 1.14) and *APOE* (ε4 = 3.81) risk alleles (Adams et al., 2015; Bertram et al., 2007), resilience to *CLU* risk required having the CC genotype. Genetic risk score (GRS) analysis was based on the cumulative risk of *APOE* and *CLU* given each alleles odds ratio. Each *APOE* ε4 allele was given a risk score of 3.81 and each *CLU* C allele was given

a risk score of 1.14, based on odds ratios generated by previous studies (Adams et al., 2015; Bertram et al., 2007). For the purposes of this study, both the *APOE* ε2 and ε3 alleles were given a risk score of 0.00. Participants were given a final GRS based on the sum of their risk conferred from ε4 and C alleles; scores ranged from 0.00 – 9.90. For example, a participant with an *APOE* ε3ε4 genotype and *CLU* TC genotype would receive a risk score of 4.95 whereas a participant with an *APOE* ε2ε3 genotype and *CLU* CC genotype would receive a risk score of 2.28. Given a maximum GRS of 9.90, we determined four levels of additive genetic risk based on quartile split (i.e., ≤ 25% = low risk, >25% to 50% = moderate-low risk, >50% to 75% = moderate-high risk, >75% = high risk). We only considered participants in the highest risk quartile as having a high GRS. Based on this definition, high GRS included: (a) carrying at least one *APOE* ε4 allele and 1-2 *CLU* C alleles or (b) carrying two *APOE* ε4 alleles and 0-2 *CLU* C alleles.

3.3. Episodic Memory Measures

We assembled a latent EM variable using three manifest indicators from the following two EM tasks. Both tasks have previously been used in the VLS (and elsewhere) and testing procedures were identical across waves.

Word recall (Dixon & de Frias, 2004; Dixon et al., 2004). Participants were asked to remember as many words as possible from a typed list of 30 English words, followed by immediate free recall. Two trials were performed. Each list consisted of six words from five taxonomic categories (e.g., flowers, birds) in random order. Participants were given two minutes to study the list and five minutes to write down as many words as they could remember. In total, six equivalent lists exist and were administered such that no participant saw the same list twice over three waves (in order to minimize practice effects). Each participant-specific score was the average number of words correctly recalled across the two lists (maximum score of 30).

Rey Auditory Verbal Learning Test (RAVLT) (Lezak, 1983; Vakil & Blachstein, 1993). Participants listened to fifteen nouns read aloud and immediately recalled, aloud, as many of the nouns as possible. This procedure was repeated five times (A1-A5). A second list (B1) of fifteen unrelated nouns was then read aloud and the participants recalled as many as possible. Finally, participants were asked to recall as many words as possible from the first list (A6). The number of nouns recalled from B1 was used as a measure of free recall, with a total score out of 15. The number of nouns recalled from A6 was used as a measure of recall after interference, with a total score out of 15 (McFall et al., 2015).

3.4. Twenty-two Risk and Protective Factors from Five Domains

For the purposes of this study, each of the 22 factors was collected from, or reported by, participants at their respective baseline: Sample 1 Wave 6, Sample 2 Wave 7, and Sample 3 Wave 1. We tested 22 factors for their ability to predict memory resilience (2 unmodifiable [age and education] and 20 modifiable).

3.4.1. Demographic Factors

Demographic data were collected by having participants fill out the VLS Personal Data Sheet. We examined five demographic factors. Although the aim of this study was to focus on modifiable predictors of resilience to AD genetic risk, we included age and education to (a) assess their relative strength with respect to other, modifiable factors and (b) completely account for their effect on other factors within our models. For example, had we not included age in our prediction models, other factors that are highly influenced by age (e.g., pulse pressure) may have differentiated groups based on age effects as opposed to memory resilience.

Age. The specific (i.e., to the decimal) age of each participant was calculated based on their date of birth and date of testing at each wave of testing. Age at each wave was used in memory trajectory analyses. Baseline age was tested as a predictor of memory resilience.

Education. Participants self-reported the number of years of education they completed. Baseline level of education was (a) used as a covariate in memory trajectory analyses and (b) tested as a predictor of memory resilience.

Marital status. Participants reported whether they were currently unmarried (coded as 0) or married (coded as 1). Being unmarried included for any reason (e.g., divorced, widowed, single).

Living status. Participants reported their current living arrangement. Participants that were not currently living with someone were coded as 0. Those that were living with someone (e.g., spouse, family member, caregiver) were coded as 1.

Pet ownership. Participants that reported owning a pet (of any kind) at baseline were coded as 1. Those that reported not owning a pet were coded as 0.

3.4.2. Functional Biomarkers

Data pertaining to four functional biomarkers was collected from participants using physical in-lab tests.

Pulse pressure (PP). Blood pressure (BP) was collected eight times (four times during each of two sessions, approximately one week apart) from seated participants using an Omron Automatic Oscillometric Digital Blood Pressure monitor (MacDonald et al., 2004). Two readings were taken at the beginning of each session and two were taken at the end. The average of the eight BP readings was calculated to get an overall average BP value (systolic/diastolic) for each participant. PP was calculated as: PP = systolic BP – diastolic BP for all participants that had at

least four BP measurements. During analysis, PP (in mm Hg) was used as a continuous variable (McFall et al., 2015).

Grip strength (GS). The GS of each participants was collected over two trials as measured by a Smedley hand dynamometer. GS was measured in kilograms of force (kg/f) (MacDonald et al., 2004). The highest score obtained from the average of each hand was used in analyses, as a continuous variable.

Peak expiratory flow (PEF). Participants, while standing, were asked to take a maximally-deep breath then executive a quick, hard blow into the mouthpiece of the MiniWright Peak Flow meter. Score (in litres/minute [L/min]) was based on largest volume expired over three attempts and was analyzed as a continuous variable.

Body mass index (BMI). The height (m) and weight (kg) of each participant were measured via a wall-mounted measuring scale and digital scale, respectively. Height and weight measurements were then used to calculate each participant's BMI (as weight/height^2 in kg/m^2). BMI was used as a continuous variable during analyses.

3.4.3. Health Characteristics

We compiled data from six health characteristics (obtained via self-report and questionnaire). We originally included history of stroke (i.e., yes or no) but there were never enough participants with a history of stroke in each analytic group (i.e., < 10%) so the factor was not used in analyses.

Subjective health. Participants were asked to rate their overall health on a 5-point Likert scale ("very good" = 1, "good" = 2, "fair" = 3, "poor" = 4, "very poor" = 5) relative to a perfect state of health (Dolcos et al., 2012).

Depressive symptoms. Participants completed the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977), a 20-question scale designed to measure depressive symptoms in the general population. The CES-D has demonstrated ability to screen symptoms in older adults (Lewinsohn, Seeley, Roberts, & Allen, 1997). Responses are based on the frequency of occurrence during the past week, out of four choices: "rarely or none of the time (less than 1 day)" = 0, "some or a little of the time (1 – 2 days)" = 1, "occasionally or a moderate amount of the time (3 – 4 days)" = 2, and "most or all of the time (5 – 7 days)" = 3. Examples of questions include "I felt lonely" and "I could not get 'going'". There are four positive affect questions (e.g., "I felt hopeful about the future") and their answers were reverse-coded when determining each participant's final score (out of 60). Higher scores indicate more depressive symptoms. CES-D score was used as a continuous variable in analyses.

Diabetes. Participants self-reported whether or not they had been diagnosed with type II diabetes (yes = 1, no = 0).

Anti-inflammatory (i.e., arthritis) medication. Participants self-reported whether or not they were currently taking anti-inflammatory medication (yes = 1, no = 0).

Cholesterol medication (e.g., statins). Participants self-reported whether or not they were currently taking medication to mnage their cholesterol (yes = 1, no = 0).

History of a head injury. Participants self-reported whether or not they had a history of head injury (either "not serious" or "moderately serious" [participants that had experienced a "very serious" head injury were excluded from this study]; yes = 1, no = 0).

3.4.4. Mobility

There are two mobility measures collected by the VLS testing battery.

Timed Walk. Participants were asked to walk a distance of 20 feet as quickly (but safely) as possible (10 feet one way, cross a line, turn around, 10 feet back). Orthotic devices were acceptable. The time taken to complete the task (in seconds [s]) was used as a continuous variable in analyses.

Timed Turn. Participants were asked to make a complete 360 degree turn in place in whatever direction they were most comfortable, returning to their starting position with their toes lined up behind the starting line. They were asked to do the task as quickly as possible but not to go so fast that they would lose their balance. Orthotic devices were acceptable. The time taken to complete the task (in seconds) was used as a continuous variable in analyses.

3.4.5. Lifestyle

We assembled five relevant lifestyle factors. We originally included current smoking status (i.e., smoker or non-smoker) but there were never enough smokers in each analytic group (i.e., < 10%) so the factor was not used in analyses.

Alcohol consumption. Alcohol use was self-reported by each participant. The variable measured was current consumer (scored as 1) versus non-consumer (scored as 0).

Everyday physical activity. Engagement in physical lifestyle activities was assessed using the VLS Activity Lifestyle Questionnaire (VLS-ALQ), a 54-item self-report questionnaire that measures the frequency of participation in various activities over the past two years (Small et al., 2012). The everyday physical activity subscale includes four items. A nine-point scale was used to rate the frequency of participation: “never” = 0, “less than once per year” = 1, “about once per year” = 2, “two to three times per year” = 3, “about once per month” = 4, “two to three times per month” = 5, “about once per week” = 6, “two to three times per week” = 7, “daily” = 8 (Small et

al., 2012). The scores were summed across the items within each subdomain, creating a maximum score of 32. Total score was used as a continuous variable.

Everyday novel cognitive activity. Another subdomain included in the VLS-ALQ is everyday novel cognitive activity (e.g., playing bridge, doing taxes, learning a language) [n = 27]), which is differentiated from passive and integrative cognitive activity subscales. The same nine-point scale described above was used to rate the frequency of participation. The scores were summed across the items within each subdomain, creating a maximum score of 216. Total score was used as a continuous variable.

Social visits. We used one specific question within the social activity subdomain of the VLS-ALQ to assess the frequency of social visits (i.e., "How often do you visit family, friends, or neighbors?"). The same nine-point scale described above was used to rate the frequency of participation therefore the maximum score was 8. Total score was used as a continuous variable.

Volunteering. We used another specific question with the social activity subdomain of the VLS-ALQ to assess frequency of volunteer activity (i.e., "How often do you volunteer?"). The same nine-point scale described above was used to rate the frequency of participation therefore the maximum score was 8. Total score was used as a continuous variable.

3.5. Statistical Analyses

3.5.1. Data preparation

IBM SPSS 23.0 for Windows (IBMCorp., 2015) was used to combine datasets for the source sample of 642 older adults. We included the EM measures at all three time-points, sex, the twenty-two risk and protective factors at baseline, and genetic data. Missing values were coded '99999'.

3.5.2. Episodic Memory Latent Variable, Measurement Invariance, and Growth Model

Foundational statistical analyses included confirmatory factor analysis and latent growth modeling. Model fit for all analyses was determined using the following standard indices: (a) chi-square test of model fit (χ^2) for which a good fit would produce a non-significant outcome ($p > 0.05$), indicating that the data are not significantly different from the estimates associated with the model, (b) Akaike Information Criterion (AIC) for which better fit is associated with a lower value, (c) Bayesian Information Criterion (BIC; which is the sample-size adjusted value of AIC and is defined as $-2\log L + p\log n$ [where p is the number of parameters and n is the sample size]), lower values imply better model fit, (d) root mean square error of approximation (RMSEA) for which a value of ≤ 0.05 is deemed good fit and ≤ 0.08 is deemed adequate fit, (e) comparative fit index (CFI) for which a value of ≥ 0.95 is deemed good fit and ≥ 0.90 is deemed adequate fit, and (f) standardized root mean square residual (SRMR), for which good fit is judged by a value of ≤ 0.08 (Kline, 2011; Little, 2013).

For these foundational analyses, we used Mplus 7.4 (Muthén & Muthén, 1998-2012). We first conducted confirmatory factor analysis. We tested a one-factor latent variable reflecting contributions from the three EM manifest indicators. We then tested longitudinal (three-wave) measurement invariance, including: (a) configural invariance (the same indicator variables load onto the latent variable at each time point), (b) metric invariance (factor loadings are constrained as equal for each latent variable to indicate that it is measuring the same construct), (c) scalar invariance (indicator intercepts are constrained to be equal which allows mean differences to be evident at the latent level), and (d) residual invariance (indicator intercepts are constrained to be equal to account for error variability so group differences are based on common variability) (Little, 2013). We estimated EM factor scores in Mplus and used them in subsequent latent

growth models. We used multiple imputations to estimate any missing EM values at all three waves. Specifically, we ran models with 50 datasets and pooled parameter sets across them. Mplus robustly produces estimates of missing data using maximum likelihood methods (Terrera et al., 2010).

To examine change patterns for the EM latent variable we used latent growth modelling. We centered age at 75 years (the approximate mean of the 40-year span of data) and used age as the metric of time. Using age in this manner accounted for the variability associated with age as if it were a covariate. Our combined EM performances across multiple cohorts of longitudinal participants produced an accelerated longitudinal design with a 40-year band of aging. We established the best fitting model by testing, in sequence: (a) a fixed intercept model (assumes no inter- or intra-individual variation), (b) a random intercept model (assumes no intraindividual change but models interindividual variability), (c) a random intercept fixed slope model (allows interindividual variation in level, but assumes all individuals change at the same rate, and (d) random intercept random slope model (allows interindividual variation in initial level and change (Singer & Willett, 2003)

3.5.3. Growth Mixture Modelling

Conventional growth modelling assumes that all participants have the same expected trajectory with random individual variation across intercept and slope. Group-based trajectory models employ multiple classes (by introducing a categorical latent variable C), each with their own trajectory, to capture variation within a sample (Kreuter & Muthén, 2008). In other words, group-based modelling is a person-centered technique that allows for the post-hoc parsing of individual trajectories based on similarities over time due to the underlying assumption that each individual belongs to a latent class (Leoutsakos, Muthen, Breitner, & Lyketsos, 2012; Ram &

Grimm, 2009). We considered two main types. Latent class growth analysis (LCGA) and Growth Mixture Modelling (GMM). LCGA models assume variation across individuals is explained by group membership (which have different developmental pathways) such that there is zero within-class variance in intercept or slope. Fixing the intercepts and growth terms to zero in this way allows for fast and clear identification of classes. GMM also identifies sub-groups of participants but allows for the intercept and slopes to have random effects (i.e., non-zero variances) (Kreuter & Muthén, 2008). If all the variances in a GMM model are constrained to zero, the results are the same as that of a LCGA model. Therefore, LCGA is a special (i.e., fully constrained) case of GMM. In both instances, each participant is assigned an estimated probability of belonging to each specified class. Generally, analysts start with LCGA models then move to GMM to determine the best-fitting multiple (or single) trajectory model (Jung & Wickrama, 2008). See Figure 3.1 for a comparison of LCGA and GMM path diagrams (Feldman, Masyn, & Conger, 2009).

We systematically tested a series of LCGA and GMM models to determine which model optimally identified subgroups (i.e., phenotypes) of older adults based on their baseline EM performance and longitudinal trajectory. Wave was not used as the metric of longitudinal change; instead, age was used centered at 75 years (McFall et al., 2016; Terrera et al., 2010). Using age in this manner allowed us to account for variability associated with age in a similar manner to being a covariate in the model. We first compared fully constrained, linear 2- and 3-class LCGA models with the most parsimonious one-class model (with and without education as a covariate). We then tested 1- to 3-class GMM models for which education was a covariate (affecting class membership) in all models. For each GMM model, we tested: (a) freed intercept variances, (b) freed slope variances, and (c) freed intercept and slope variances. For both LCGA

and GMM, quadratic models had significantly worse fit than the linear models and demonstrated convergence problems which is typical with only three waves of data. As such, we did not report the quadratic model statistics and will not discuss them further.

Mplus incorporates random starts to avoid problems, such as convergence issues or hitting local maxima, which are associated with LCGA and GMM models. To ensure the solution was not local, we replicated the maximum for multiple random starts. We used 100 random starting values with 10 final optimizations. If the model did not replicate the loglikelihood, we increased to 500 random starting values and 20 final optimizations, as recommended (Jung & Wickrama, 2008). We did not consider models that did not replicate their loglikelihood after increasing the number of random starting values. We confirmed each final, best-fitting model by replicating the results with the outputted optimizations.

Model Assessment and Selection

Conventional chi-square based fit indices (e.g., CFI, RMSEA) used to assess growth model fit are not available when testing more than one latent class (as there is not a single covariance matrix to fit the data) (Wang & Bodner, 2007). Instead, we used standard LCGA and GMM procedures to assess model fit (Hayden et al., 2011; Jung & Wickrama, 2008; Nylund, Asparouhob, & Muthén, 2007; Pietrzak et al., 2015; Ram & Grimm, 2009) which will now be discussed.

Comparative fit. We report AIC and BIC which account for model loglikelihood and model complexity. Although we report both values, BIC performs better and more consistently than AIC (and it penalizes more for model complexity) so we primarily used it for model comparison (Kreuter & Muthén, 2008). The BIC is also preferred over other model statistics that are sensitive to sample size (which can lead to interpretation bias) (Hox & Bechger, 2007). A

lower value indicated better model fit. We also report -2 loglikelihood (-2LL), which is -2 x the loglikelihood of the restricted model minus the loglikelihood of the unrestricted model. Again, lower values indicate better model fit.

Entropy. Entropy measures the precision of classification—higher entropy indicates clearer class separation. In other words, entropy indicates how well group membership can be predicted using the observed data. Values ranges from 0 to 1. Although not a measure of model fit or intended for model selection (Ramaswamy, Desarbo, Reibstein, & Robinson, 1993), extremely low values indicate that the model may too poor to distinguish homogenous groups of participants. There are no set cut-off criteria for entropy, however values of around 0.80 or higher are preferred. Entropy values > 0.6 represent at least 80% correct assignment of participants (Lubke & Muthén, 2007) and indicate the model has reasonable classification of participants into their classes (Lenehan et al., 2015)

Proportion. One important consideration when determining the best mixture model is that there should be no less than 1% of the sample in a class (Jung & Wickrama, 2008). In other words, LCGA or GMM models that determine a class with a proportion less than 0.010 should be discarded in favor of a different model. Because we performed additional analyses with the classes obtained, we did not consider models with a latent class that included a proportion of < 10% of subjects (Uher et al., 2010).

Probability. High posterior probabilities (i.e., near 1.00) are ideal.

Convergence. Models that did not converge, even after increasing the number of random starts (which suggests the model's parameter estimates are untrustworthy), were not considered further.

Plots. Visual inspection of graphical model fit and classes aids in the judgement of model fit and class separation (e.g., do the results make theoretical sense?) and should be considered in terms of theory and interpretability (Feldman et al., 2009; Kok et al., 2015). We created spaghetti plots for the classes identified.

3.5.4. One-way Analysis of Variance and Chi-Square Tests

We employed multiple one-way analysis of variance (ANOVA) tests using IBM SPSS 23 (IBMCorp., 2015). The purpose of these analyses was to provide a baseline comparison in two cases. The first case was to determine if differences in baseline factors exist between females and males. The second case was to compare risk factor values between (a) females resilient and non-resilient to the *APOE* ε4 allele, (b) males resilient and non-resilient to the *APOE* ε4 allele, (c) females resilient and non-resilient to the *CLU* CC genotype, (d) males resilient and non-resilient to the *CLU* CC genotype, (e) females resilient and non-resilient to a high GRS, and (f) males resilient and non-resilient to a high GRS. The independent variable (e.g., resilience status) was a between-subjects factor with two levels (e.g., resilient versus non-resilient). The dependent variable was a characteristic from each domain. For categorical variables, we used chi-square (χ^2) tests. P-values were not reported for χ^2-tests in which the expected cell count was too low (i.e., < 5). For all continuous variables, outcomes that were more than 3 SD above or below the mean were considered outliers and were removed before ANOVA tests. We emphasize that these tests are not the main focus of this study. As such, ANOVA and χ^2-tests results are not described or discussed in the subsequent sections of this thesis. We report means and standard deviations (or percentages, where applicable) for each factor within each group to enhance interpretability of the remaining analyses.

3.5.5. Random Forest Analysis

To determine which of the 22 factors were the most important predictors of memory resilience, we used Random Forest Analysis (RFA)—a recursive partitioning multivariate data exploration technique with robust ability to cope with large numbers of predictor variables (Breiman, 1996, 2001; Strobl et al., 2009). RFA is based on the assembly of a set of classification and regression trees (CART). CART utilizes a nonparametric regression approach wherein a predictor value that most effectively partitions the data into two distinct groups is used at each split (Kuhn & Johnson, 2013). Each tree is independent and composed of a bootstrap sample of random data and predictor variables. For each predictor, the tree finds the distinct value that partitions the data into two groups (minimizing the overall sum of squares). At each new node the predictor most strongly associated with the outcome is selected for the next split. Thus, as more predictor variables are used in the tree (recursive partitioning), each split results in nodes that are more homogeneous and distinct from each other (an example is presented in Figure 3.2). CART can handle both categorical and continuous predictor variables—even if they are skewed, sparse, or contain missing values (Kuhn & Johnson, 2013). Therefore, data pre-processing is minimal.

However, single trees demonstrate instability in classification and poor predictive power. By combining an ensemble of trees (to create a "forest"), prediction variation is substantially reduced. RFA simultaneously processes large number of variables through bootstrap aggregation of single trees to combine the predictions of many trees. This procedure (a) improves model stability, (b) improves prediction accuracy, (c) reduces bias, and (d) negates risk of overfitting (Strobl et al., 2009). Notably, because each tree is created from an arbitrary selection of predictors and participants, there is considerable randomness in the tree construction process

which (a) reduces correlation among predictors and trees (Kuhn & Johnson, 2013) and (b) can give high importance scores to variables involved in complex interactions that would have otherwise gone unnoticed (Strobl et al., 2009). RFA is suitable for (a) datasets with a large number of predictors even when the sample size is relatively small in comparison (e.g., when logistic regression would not be possible) and (b) testing a number of predictors that may be correlated (Strobl, Boulesteix, Zeileis, & Hothorn, 2007). RFA robustly adapts to sparsity; that is, rate of convergence in RFA depends on the number of strong features, not on how many noise variables are present (Biau, 2012).

Further diversity is introduced to RFA models by specifying (a) *mtry,* or the number of randomly selected predictor variables used to create each tree and (b) *ntree*, or the overall number of trees. Restricting the number of predictor variables used in each tree can reveal important variables that would have otherwise been overshadowed by a stronger competitor. By combining the predictions of all the individual trees, RFA provides a ranked order of variable importance (Strobl et al., 2009). *Ntree* values are recommend to start at 1000 but can be increased if it improves the area under the receiver operating characteristic curve (C-statistic) as RFA is protected from over-fitting (Kuhn & Johnson, 2013). Generally, mtry is set at $\sqrt{\#\ of\ predictors}$ (Genuer, Poggi, & Tuleau-Malot, 2010).

RFA produces an internal estimate of its predictive performance. Misclassification rates (area under the receiver operating curve) are assessed with cross-validation (out-of-bag [OOB] error rate). Briefly, a random two thirds of the sample is used to construct a tree with a random sample of predictors. The outcome of the remaining one third of the sample (OOB) is predicted using the tree to determine the misclassification rate (Kuhn & Johnson, 2013). The OOB error for that specific tree and variable importance for each factor in the tree are aggregated across all

trees in the model to determine the overall model OOB error rate (i.e., percentage of misclassification) and overall variable importance score for each factor.

We conducted RFA using R 3.2.5, a free software environment and programming language for statistical computing (R Development Core Team, 2015). User-created packages extend the usability of R to include specialized statistical techniques, tools, or graphical devices. Before RFA, we enhanced model performance with two R packages. Although missing predictor data were minimal (< 1%), we imputed missing values using the missForest package (Stekhoven & Bühlmann, 2012; Waljee et al., 2013). We also balanced the datasets using the Synthetic Minority Over-sampling Technique (SMOTE) operation in the DMwR package (Chawla, Bowyer, Hall, & Kegelmeyer, 2002; Torgo, 2010). SMOTE over-samples the minority class (by introducing synthetic examples based on *k-nearest neighbor* classification and bootstrapping) and down-samples the majority class, if required. Three main parameters exist for the SMOTE function in the DMwR package: *k-nearest neighbor*, *perc.under* (percentage of under-sampling), and *perc.over* (percentage of over-sampling). In all SMOTE calculations, the *k* value was set to the default value of 5. We set our SMOTE controls to obtain balanced datasets with minimal loss of the majority class (see Table 3.3).

To perform RFA (i.e., determine which factors were the best predictors of EM resilience), we installed and used the "Party" package (Hothorn, Buehlmann, Dudoit, Molinaro, & Van Der Laan, 2006). Each forest was composed of *ntree* = 5000 trees (which is sufficient for good model stability). At each potential split we evaluated a random sample of *mtry* = 5 predictors (the square root of the number of predictors rounded up to the nearest integer value) (Guo, Graber, McBurney, & Balasubramanian, 2010). Of note, when predictors vary in scale of measurement and number of categories, RFA may favor variables with many possible cut points

(e.g., continuous variables are favored over categorical). However the RFA *cforest* function in the Party package uses an adequate resampling scheme to negate that risk (Kuhn & Johnson, 2013). Categorical variables with too few cases in the minority cell (i.e., < 10%) for each sex x genetic risk group were eliminated for a specific analysis (n=9). The nine cases included: diabetes status for female *APOE* ε4 carriers and females with a high GRS; arthritis medication for all three male genetic risk groups; head injury for male ε4 carriers and males and females with a high GRS; and alcohol use for male *CLU* C homozygotes.

Factors were ranked by the advanced variable importance measure permutation accuracy importance, which reflects the relative strength of each variable in predicting the outcome (i.e., resilience or non-resilience). Briefly, each factor used to construct the tree is permuted and the OOB error rate is recomputed. The permuted variable's OOB (prediction accuracy) is compared to the original OOB error. A large difference in prediction accuracy would mean the variable is important whereas a small difference in prediction accuracy following permutation would mean the variable is unimportant. Predictors are considered unimportant and can be excluded from further exploration if they obtain an importance value that is (a) negative, (b) zero, or (c) a small positive value within the same range as the negative values. Strobl and colleagues (2009) suggest that absolute values of importance variables not be compared, and instead urge readers to rely on a descriptive ranking of the predictor variables. As has been done previously (Kaup et al., 2015), we used these criteria for considering a variable to be an important predictor of resilience.

Table 3.1. Study sample demographic and retention data by wave and sex.

	Wave 1	Wave 2	Wave 3	W1-W2	W2-W3
Females					
N Sample 1	42	35	0	83.3%	-
N Sample 2	111	86	0	77.5%	-
N Sample 3	273	228	207	83.5%	90.8%
Age	70.05 (8.91)	74.24 (8.77)	74.59 (7.38)		
Education	14.85 (2.88)	15.13 (2.87)	15.15 (2.98)		
Males					
N Sample 1	17	14	0	82.4%	-
N Sample 2	71	58	0	81.7%	-
N Sample 3	128	108	97	84.3%	89.8%
Age	72.01 (8.13)	76.24 (7.97)	76.65 (7.46)		
Education	15.94 (3.00)	15.84 (3.20)	15.93 (3.26)		

Note. Age and education, in years, are presented as *Mean (Standard Deviation)*.
Abbreviations: W1-W2, Wave 1 to Wave 2; W2-W3, Wave 2 to Wave 3; *N*, sample size.

Table 3.2. Observed genotypic frequencies compared to expected genotypic frequencies based on Hardy-Weinberg equilibrium analyses.

Gene, SNP	Genotype	Expected *n*	Observed *n*
APOE	ε2ε2, ε2ε3, ε3ε3	465.2	463
rs429358;	ε2ε4, ε3ε4	162.6	167
rs7412	ε4ε4	14.2	12
CLU	CC	220.6	216
rs11136000	CT	310.9	320
	TT	109.6	105

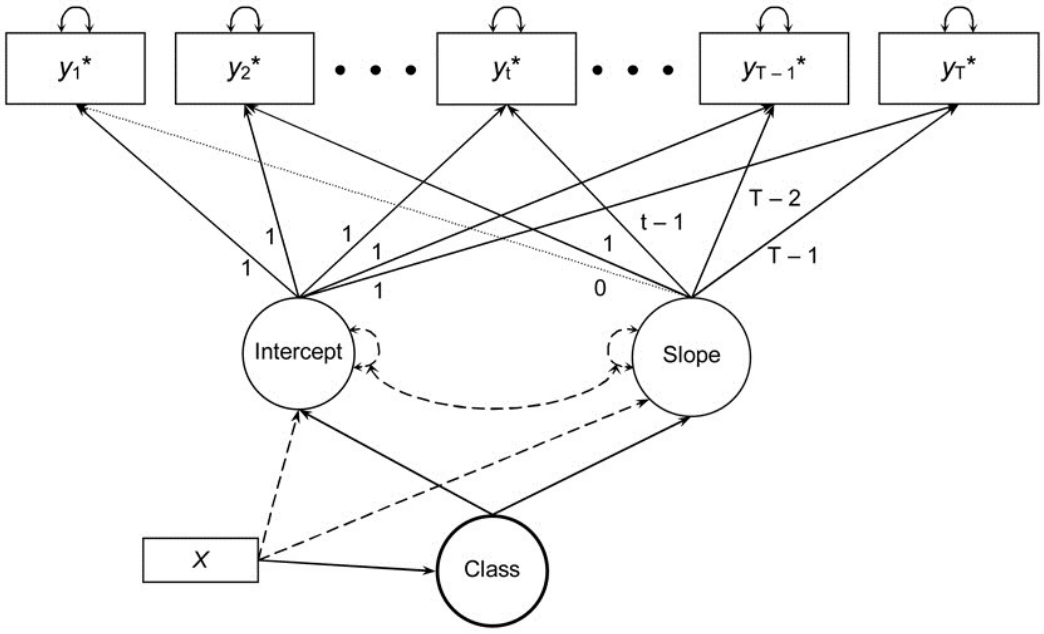
Note. Abbreviations: SNP, single nucleotide polymorphism; *APOE*, Apolipoprotein E; *CLU*, Clusterin; ε2, epsilon 2 allele; ε3, epsilon 3 allele; ε4, epsilon 4 allele; C, Cytosine; T, Thymine.

Table 3.3. Synthetic Minority Oversampling Technique (SMOTE) ratios employed in order to balance sample sizes prior to random forest analysis.

	***APOE* ε4 Carriers**		***CLU* C Homozygotes**		**High GRS**	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Unbalanced Model						
N Resilient	76	34	112	24	68	27
N Non-resilient	43	26	41	39	31	22
Model C-statistic	0.73	0.72	0.78	0.69	0.70	0.68
Balanced Model						
perc.over:*perc.under*	80:225	25:550	200:137	50:300	100:220	40:340
N Resilient	76	33	112	36	62	27
N Non-resilient	77	32	123	36	68	30
Model C-statistic	0.82	0.78	0.91	0.77	0.80	0.78

Note. Abbreviations: *APOE*, Apolipoprotein E; *CLU*, Clusterin; ε4, epsilon 4 allele; C, Cytosine; GRS, genetic risk score; *perc.over:perc.under*, percentage of over-sampling and percentage of under-sampling; *N*, sample size; C-statistic, area under the receiver operating characteristic curve.

Growth Mixture Modelling



Latent Class Growth Analysis

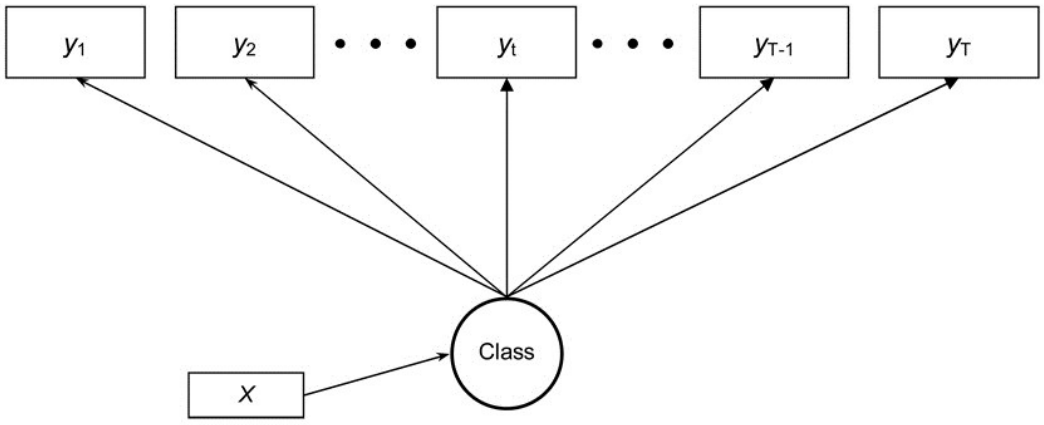


Figure 3.1. Path diagrams for growth mixture modeling and latent class growth analysis with a covariate ('x'). From Feldman et al. (2009).

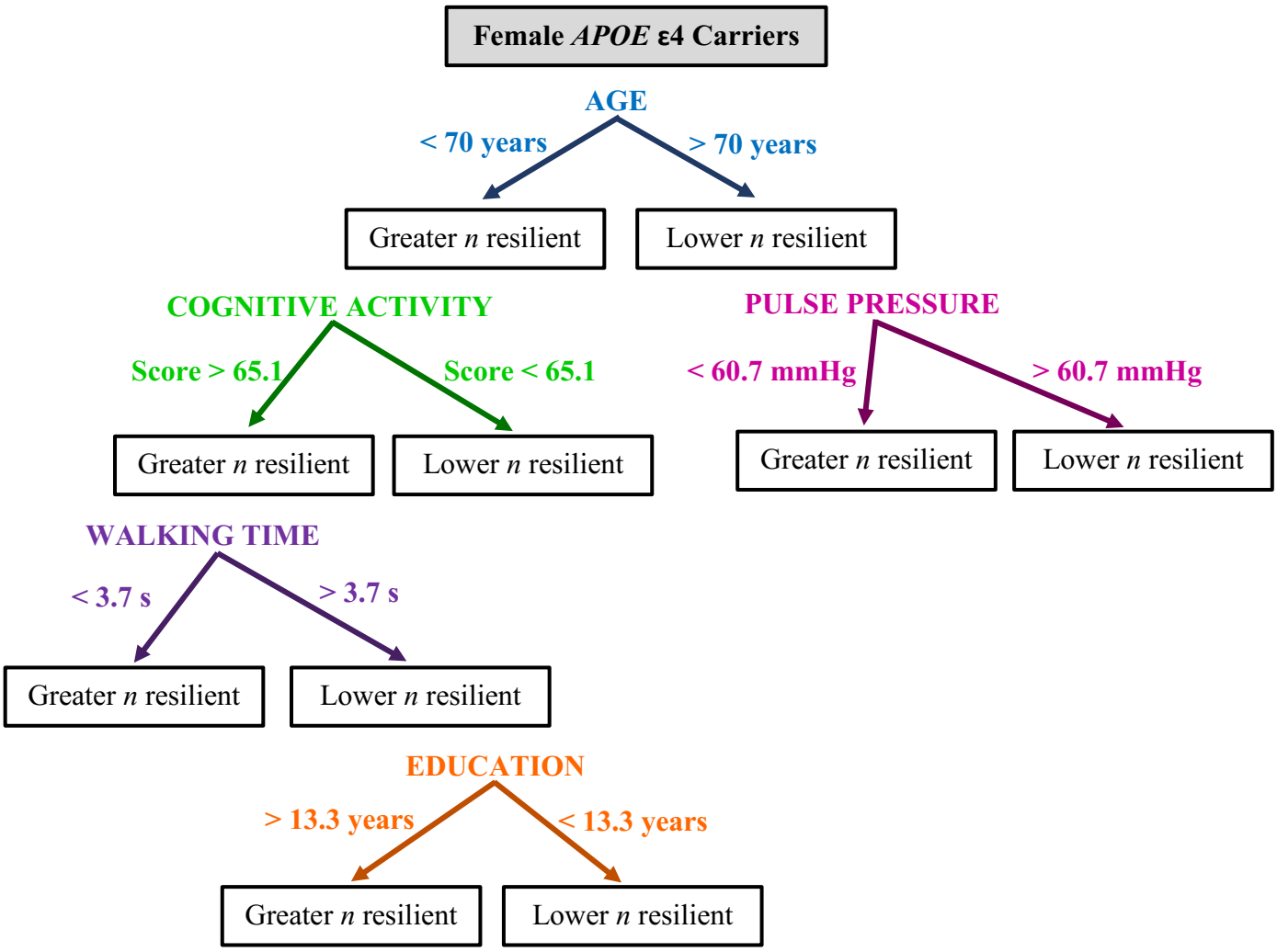


Figure 3.2. A hypothetical example of how a classification and regression tree (with *mtry* = 5) may look.

Chapter 4 – Results

4.1. Episodic Memory Latent Variable, Measurement Invariance, and Growth Model

We performed confirmatory factor analysis for EM and determined that the single factor EM model fit the data well. We then conducted measurement invariance testing (Table 4.1). There was support for configural and metric invariance. Our test for scalar invariance resulted in significantly poorer model fit so we conducted tests of partial scalar invariance by freeing intercepts for each indicator in turn. Despite a significant decrease in model fit, we retained the partial scalar model given the pattern of good fit indices as has been done previously with this VLS sample (e.g., McFall et al., 2015). Our optimal model had the Word Recall indicator invariant and the RAVLT B1 and A6 indicators free to vary across time. Because we did not observe full scalar invariance, we did not test for invariance of residual variances. In sum, results from invariance testing showed that our model measured the same EM construct across time and the same indicator variables marked EM at each wave. Partial scalar invariance allowed us to compare latent variable means, but the manifest variables had some longitudinal mean differences outside latent differences. The results permit further analyses of the EM latent variable.

To determine how EM changed across time, we tested latent growth models using the estimated factor scores and with age (centered at 75) as the metric of time. The EM factor score skewness at each wave ranged from -0.374 to -0.433 and kurtosis ranged from 0.059 to 0.250 indicating that the data were approximately normally distributed (George & Mallery, 2010). The best fitting model was a random intercept, random slope latent growth model (Table 4.1). We observed that individuals varied in performance at age 75 (b = 0.900, p = 0.000), exhibited

significant decrease in EM performance (M = -0.023 , p = 0.000), and showed variable patterns of decrease (b = 0.002, p = 0.000).

4.2. Test Genetic Risk for Episodic Memory Decline

Before conducting our primary analyses, we determined whether *APOE* ε4 status, the *CLU* CC genotype, and a high GRS were risk factors for EM impairment and decline among females and males.

For females, *APOE* risk status (ε4+ vs ε4-; n = 426) did not exhibit differential patterns in EM at age 75 (β_i = -0.124 [0.105], p = 0.237) but did exhibit differential patterns in EM change (β_s = -0.014 [0.006], p = 0.015). *CLU* genotype (CC vs TC and TT; n = 425) did not exhibit differential patterns in EM at age 75 (β_i = 0.081 [0.105], p = 0.443) but exhibited differential patterns in EM change in the unexpected direction (β_s = 0.013 [0.006], p = 0.047). GRS (continuous; based on ε4 and C as risk alleles; n = 425) did not exhibit differential patterns in EM at age 75 (β_i = -0.015 [0.025], p = 0.534) or change in EM (β_s = -0.002 [0.001], p = 0.271).

For males, we observed no significant independent genotype or GRS association with EM performance or decline (*APOE* β_i = -0.112 [0.133], p = 0.399, β_s = -0.005 [0.009], p = 0.558; *CLU* β_i = -0.111 [0.135], p = 0.411, β_s = -0.014 [0.009], p = 0.123; GRS β_i = -0.006 [0.026], p = 0.814, β_s = -0.001 [0.002], p = 0.789; all n = 216).

4.3. Growth Mixture Modelling

Based on prior research (e.g., Zahodne et al., 2015) and our sample size restrictions, we tested one-, two-, and three-class LCGA and GMM models. Generally, more classes are needed to optimally characterize variation using LCGA (compared to GMM) given that individual differences are modeled by class membership only (Feldman et al., 2009). Therefore, we expected the best-fitting LCGA model to contain more classes than the best-fitting GMM model.

When comparing model fit, the model with the smallest BIC was preferred (Geiser, 2013). We used additional model fit statistics and considerations as necessary.

Females (see Table 4.2). Of the LCGA models, the 3-class model with education as a covariate fit the data best (BIC = 1838.0). In most cases, the GMM models provided even better fit. The best-fitting GMM model was the 2-class model with estimated intercept variance (BIC = 1347.5). Although the 2- and 3-class models with estimated intercept and slope variances fit the data better (BIC = 1322.7 and 1317.5, respectively), both resulted in a class with proportion < 10% so they were not considered further. Finally, the 3-class model with estimated intercept variance had a better BIC (1317.0) than the 2-class model but the loglikelihood was not replicated and one class had a proportion < 10% so it was not considered further.

Males (see Table 4.3). Of the LCGA models, the 3-class model with education as a covariate fit the data best (BIC = 852.5). In most cases, the GMM model provided even better fit. The best-fitting GMM model was the 2-class model with estimated intercept variance (BIC = 654.3). Although both the 2- and 3-class models with estimated intercept and slope variances fit the data better (BIC = 647.0 and 645.1, respectively) both resulted in a class with proportion < 10% so they were not considered further.

For both females and males, each two-class model consisted of a class of participants characterized by (a) higher baseline performance (level; M_I) and stable trajectory (slope; M_S) of EM scores (hereafter defined as "higher-performing") and (b) lower baseline performance and declining trajectory of EM scores (hereafter defined as "lower-performing"). Higher-performing females had a M_I = 0.599 (SD = 0.057) and M_S = -0.003 (SD = 0.003); lower-performing females had a M_I = -0.624 (SD = 0.0.072) and M_S = -0.065 (SD = 0.005) (Table 4.4, Figure 4.1). Higher-performing males had a M_I = 0.077 (SD = 0.093) and M_S = 0.010 (SD = 0.004); lower-

performing males had a M_I = -0.895 (*SD* = 0.094) and M_S = -0.066 (*SD* 0.005) (Table 4.4, Figure 4.2).

4.4. Analysis of Variance and Chi-square Tests

Descriptive sex differences. Significant sex differences for level of performance or response were observed for multiple factors across all five risk domains (Table 4.5). Specifically, males: (a) were older (M_F = 70.1, M_M = 72.1, p = 0.005), (b) were more highly educated (M_F = 14.9, M_M = 15.9, p = 0.000), (c) were more likely to be married ($\%_F$ = 47.9, $\%_M$ = 86.6, p = 0.000) and/or living with someone ($\%_F$ = 54.5, $\%_M$ = 88.4, p = 0.000), (d) had higher pulse pressure (M_F = 51.3, M_M = 52.9, p = 0.049), (e) had greater peak expiratory flow (M_F = 372.4, M_M = 523.5, p = 0.000), (f) had stronger grip (M_F = 24.2, M_M = 39.4, p = 0.000), (g) were more likely to be taking cholesterol-lowering medication ($\%_F$ = 10.1, $\%_M$ = 16.7, p = 0.022), (h) had faster walking times (M_F = 6.5, M_M = 6.0, p = 0.000), (i) were more physically active (M_F = 15.4, M_M = 16.4, p = 0.030), (j) were more cognitively active (M_F = 73.3, M_M = 78.5, p = 0.000), and (k) had less social visits with family, friends, and neighbors (M_F = 5.6, M_M = 5.1, p = 0.000) than females. Approaching significance, males (a) were more likely to be diabetic ($\%_F$ = 5.9, $\%_M$ = 10.2, p = 0.055) and (b) volunteered less often (M_F = 3.8, M_M = 3.2, p = 0.074) than females.

4.5. Random Forest Analysis

The sample sizes for each sex x genetic risk before and after SMOTE were presented in Table 3.3. As indicated, RFA model C-statistics improved for all models following SMOTE (showing good to very good classification performance: 0.77 - 0.91) and we proceeded to use the balanced models as recommended (Torgo, 2010).

Important Predictors of Resilience by Sex

Prediction analyses for APOE*-based resilience groups:* Memory trajectories for resilient and non-resilient females and males carrying an ε4 allele are presented in Figures 4.3-4.4. As can be seen in Figures 4.5-4.6, we observed that four predictors were common to males and females. The demographic variables age and education emerged within the top three overall most important predictors of resilience in both sexes. From the functional biomarker domain, GS was an important predictor of resilience. From the lifestyle domain, everyday novel cognitive activity was a top predictor of resilience for both sexes. Predictors of resilience specific to females arose from the demographic (i.e., living status and marital status), functional biomarker (i.e., PEF and PP), health (i.e., subjective health), mobility (i.e., timed turn and timed walk), and lifestyle (i.e., volunteering and social visits) domains. Males had one unique predictor of resilience from the health domain (i.e., CES-D score). For full results see Tables 4.6-4.7.

Prediction analyses for CLU*-based resilience groups:* Memory trajectories for resilient and non-resilient female and male *CLU* C homozygotes are presented in Figures 4.7-4.8. As can be seen in Figures 4.9-4.10, we observed that six predictors were common to both males and females. The demographic variables age and education predicted resilience for both sexes. Both demographic factors were of high importance, with the exception of age in females which was lower in the predication hierarchy. One functional biomarker (GS) and three lifestyle characteristics (everyday cognitive activity, volunteering, and social visits) predicted resilience in both sexes. However, more participation in both social lifestyle activities predicted resilience in females whereas less participation predicted resilience in males. Predictors of resilience specific to females arose from the demographic (i.e., marital status and living status), functional biomarker (i.e., PP, PEF, and BMI), health (i.e., subjective health, and arthritis medication),

mobility (i.e., timed walk and timed turn), and lifestyle (i.e., current alcohol use) domains. Males had two unique predictors of resilience from the demographic (i.e., pet ownership) and health (i.e., CES-D score) domains. For full results see Tables 4.8-4.9.

Prediction analyses for GRS-*based resilience groups:* Memory trajectories for resilient and non-resilient females and males with a high GRS are presented in Figures 4.11-4.12. As can be seen in Figures 4.13-4.14, we observed that five predictors were common to both males and females. The demographic variables age and education predicted resilience for both sexes and both were of high importance. Two functional biomarkers (i.e., GS, PEF) and one lifestyle factor (i.e., everyday novel cognitive activity) predicted resilience in both sexes. Predictors of resilience specific to females arose from the demographic (i.e., living and marital status), functional biomarker (i.e., PP, BMI), health (i.e., subjective health), mobility (i.e., timed walk and timed turn), and lifestyle (i.e., social visits, volunteering) domains. Males did not have any unique predictors of resilience. For full results see Tables 4.10-4.11.

Generalizability of Predictor Patterns across Genetic Risk

Among females, 18 (85.7%) of the 21 predictors tested in the *APOE* and *CLU* risk groups were genetically robust. Specifically, 13 factors were reported as important predictors of both *APOE*-, and *CLU* -based resilience and three factors were unimportant. The 13 important and genetically robust predictors arose from demographic (i.e., age, education, marital status, and living status), functional biomarker (i.e., PP, PEF, and grip strength), health (i.e., subjective health), mobility (i.e., turning time and walking time), and lifestyle (i.e., everyday cognitive activity, social visits, and volunteering) domains. Notably, the top predictors had different relative importance for *APOE*- versus *CLU*-based resilience. Three factors were only important predictors of resilience to the *CLU* CC genotype: lower BMI, taking arthritis medication, and

current alcohol use. All of the genetically robust predictors of resilience for females were matched in GRS-based resilience analyses. The relative importance of the predictors in GRS-based analyses was most similar to that of predictors for *APOE*-based resilience. Of the predictors specific to *CLU*-based resilience, lower BMI also predicted resilience to a high GRS. See Figure 4.15 for a visual comparison of predictors by sex and genetic risk.

Among males, 16 (84.2%) of the 19 predictors tested in the *APOE* and *CLU* risk groups were genetically robust. Specifically, five factors were reported as important predictors of *APOE*- and *CLU*-based resilience and 11 factors were unimportant. The important and genetically robust predictors arose from demographic (i.e., age and education), functional biomarker (i.e., grip strength), health (i.e., CES-D score) and lifestyle (i.e., everyday cognitive activity) domains. One demographic factor (i.e., pet ownership) and two lifestyle factors (i.e., less social visits and volunteering less often) predicted resilience to the *CLU* CC genotype only. The majority of the genetically robust predictors of resilience for males were matched in the GRS-based resilience analyses. However, higher CES-D score was not an important predictor of GRS-based resilience. Additionally, PEF emerged as an important predictor of resilience to a high GRS. See Figure 4.15 for a visual comparison of predictors by sex and genetic risk.

Table 4.1. Goodness of fit indexes for episodic memory models confirmatory factor analyses and latent growth models.

Model	AIC	BIC	X^2	df	*p*	RMSEA	CFI	SRMR
CFA for One Factor Model								
Configural	25963.5	26137.6	15.4	15	.421	.007 (.000-.038)	1.00	.014
Metric	25978.6	26134.9	38.5	19	.005	.040 (.021-.058)	.991	.049
Scalar	26195.9	26325.3	267.8	25	<.001	.123 (.110-.137)	.886	.106
Partial Scalar[†]	26064.5	26211.9	128.4	21	<.001	.089 (.075-.104)	.950	.091

Model	AIC	BIC	-2LL	*D*	Δdf	*p*
Latent growth model						
Fixed Intercept	4198.9	4207.8	4194.9	-	-	-
Random Intercept	2402.8	2416.2	2396.8	1798.1	1	<.001
Random Intercept Fixed Slope	2255.5	2270.4	2244.9	151.9	1	<.001
Random Intercept Random Slope*	2008.0	2034.8	1996.0	248.9	2	<.001

Note. [†] REY B1 and A6 free to vary; * best fitting model. Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; χ^2, chi-square test of model fit; df, degrees of freedom for model fit; *p*, *p*-value; RMSEA, root mean square error of approximation; CFI, comparative fix index; SRMR, standardized root mean square residual; CFA, confirmatory factor analysis; -2LL, -2 log likelihood; *D,* difference statistic (using -2LL); Δdf, change in degrees of freedom.

Table 4.2. Goodness of fit indexes for one- to three-class episodic memory Latent Class Growth Analysis (LCGA) and Growth Mixture Modelling (GMM) for females.

Model	Class	AIC	BIC	-2LL	Entropy	Prob.	Prop.	*n*
LCGA: 1-Class, no covariate	1	2532.2	2552.5	2522.2	-	1.00	1.00	426
LCGA: 1-Class, education covariate	1	2474.6	2503.0	2460.6	-	1.00	1.00	426
LCGA: 2-Class, no covariate	1	2104.3	2136.7	2111.3	0.765	0.937	0.577	246
	2					0.915	0.423	180
LCGA: 2-Class, education covariate	1	2071.6	2116.2	2049.6	0.769	0.932	0.592	252
	2					0.930	0.408	174
LCGA: 3-Class, no covariate	1	1806.4	1851.4	1784.8	0.858	0.945	0.117	50
	2					0.946	0.392	167
	3					0.922	0.490	209
LCGA: 3-Class, education covariate	1	1777.1	1838.0	1747.1	0.852	0.923	0.481	205
	2					0.939	0.399	170
	3					0.935	0.120	51
GMM: 1-Class, est. intercept variances	1	1473.9	1490.2	1465.9	-	1.00	1.00	426
GMM: 1-Class, est. slope variances	1	2436.9	2453.2	2429.0	-	1.00	1.00	426
GMM: 1-Class, est. intercept, slope variances	1	1314.3	1338.6	1302.3	-	1.00	1.00	426
GMM: 2-Class, est. intercept variances*	1	1315.1	1347.4	1299.1	0.623	0.854	0.324	138
	2					0.902	0.676	288
GMM: 2-Class, est. slope variances	1	1973.1	2005.6	1957.1	0.736	0.918	0.399	170
	2					0.925	0.601	256
GMM: 2-Class, est. intercept, slope variances	1	1282.2	1322.7	1262.2	0.913	0.887	0.023	10
	2					0.983	0.977	416
GMM: 3-Class, est. intercept variances ‡	1	1268.3	1317.0	1244.3	0.729	0.882	0.636	271
	2					0.852	0.347	148
	3					0.900	0.016	7
GMM: 3-Class, est. slope variances	1	1694.5	1743.2	1670.5	0.788	0.925	0.120	51
	2					0.877	0.465	198
	3					0.914	0.415	177
GMM: 3-Class, est. intercept, slope variances	1	1260.7	1317.5	1232.7	0.562	0.808	0.502	214
	2					0.801	0.028	12
	3					0.755	0.469	200

Note. All models are specified with a linear growth function. All growth mixture models included education as a covariate. * Best fitting model. ‡The best loglikelihood was not replicated, even after increasing the number of random starts. Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; χ^2, chi-square test of model fit; -2LL, -2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimate model; *n*, sample size; est., estimated.

Table 4.3. Goodness of fit indexes for one- to three-class episodic memory Latent Class Growth Analysis (LCGA) and Growth Mixture Modelling (GMM) for males.

Model	Class	AIC	BIC	-2LL	Entropy	Prob.	Prop.	*n*
LCGA: 1-Class, no covariate	1	1216.2	1233.1	1206.2	-	1.00	1.00	216
LCGA: 1-Class, education covariate	1	1187.6	1211.2	1173.6	-	1.00	1.00	216
LCGA: 2-Class, no covariate	1	1012.7	1039.7	996.7	0.790	0.932	0.435	94
	2					0.938	0.565	122
LCGA: 2-Class, education covariate	1	987.4	1024.6	965.4	0.787	0.943	0.556	120
	2					0.930	0.444	96
LCGA: 3-Class, no covariate	1	873.0	910.2	851.0	0.844	0.923	0.518	112
	2					0.939	0.338	73
	3					0.908	0.144	31
LCGA: 3-Class, education covariate	1	801.8	852.5	771.9	0.893	0.946	0.255	55
	2					0.952	0.486	105
	3					0.956	0.259	56
GMM: 1-Class, est. intercept variances	1	719.9	733.4	711.9	-	1.00	1.00	216
GMM: 1-Class, est. slope variances	1	1174.3	1187.8	1166.3	-	1.00	1.00	216
GMM: 1-Class, est. intercept, slope variances	1	637.5	657.7	625.5	-	1.00	1.00	216
GMM: 2-Class, est. intercept variances*	1	627.3	654.3	611.3	0.615	0.871	0.528	114
	2					0.887	0.472	102
GMM: 2-Class, est. slope variances	1	989.8	1016.8	973.8	0.707	0.903	0.481	104
	2					0.924	0.519	112
GMM: 2-Class, est. intercept, slope variances	1	613.3	647.0	593.3	0.973	0.817	0.023	5
	2					0.997	0.977	211
GMM: 3-Class, est. intercept variances ‡	1	626.5	667.0	602.5	0.571	0.777	0.097	21
	2					0.850	0.477	103
	3					0.744	0.426	92
GMM: 3-Class, est. slope variances	1	846.6	887.1	822.6	0.824	0.917	0.560	121
	2					0.925	0.120	26
	3					0.929	0.319	69
GMM: 3-Class, est. intercept, slope variances	1	597.9	645.1	569.9	0.683	0.857	0.569	123
	2					0.829	0.407	88
	3					0.883	0.023	5

Note. All models are specified with a linear growth function. All growth mixture models included education as a covariate. * Best fitting model. ‡The best loglikelihood was not replicated, even after increasing the number of random starts. Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; χ^2, chi-square test of model fit; -2LL, -2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimate model; *n*, sample size; est., estimated.

Table 4.4. Baseline characteristics for higher- and lower-performing females and males.

Characteristic	Higher-Performing Females (*n* = 288)	Higher-Performing Males (*n* = 114)	Lower-Performing Females (*n* = 138)	Lower-Performing Males (*n* = 102)
EM Performance				
Intercept	0.599 (0.057)	0.077 (0.093)	-0.624 (0.072)	-0.895 (0.094)
Slope	-0.003 (0.003)	0.010 (0.004)	-0.065 (0.005)	-0.066 (0.005)
Demographics				
Age (years)	68.02 (8.75)	69.75 (8.05)	74.29 (7.69)	74.73 (7.43)
Education (years)	15.57 (2.73)	17.21 (2.67)	13.36 (2.62)	14.53 (2.71)
Married (%)	49.7	86.0	44.2	87.3
Living with Someone (%)	57.3	88.6	48.6	88.2
Pet Ownership (%)	29.5	35.1	25.5	25.5
Functional Biomarkers				
Pulse Pressure (mm Hg)	49.94 (9.75)	51.55 (9.49)	54.16 (9.30)	54.49 (9.81)
Peak Flow (L/min)	378.64 (79.59)	540.32 (101.45)	358.81 (86.45)	504.54 (110.29)
Grip Strength (kg/f)	24.79 (4.95)	41.21 (7.41)	23.06 (4.79)	37.30 (7.39)
Body Mass Index (kg/m^2)	26.69 (4.32)	26.88 (3.14)	26.90 (4.32)	27.05 (3.56)
Health				
Subjective Health*	1.79 (0.71)	1.72 (0.69)	1.95 (0.80)	1.77 (0.70)
Depression (CES-D)	8.77 (5.16)	7.42 (3.82)	9.43 (5.76)	8.37 (4.74)
Diabetes (% with)	5.2	6.1	7.2	14.7
Statins (% taking)	9.1	18.4	12.3	14.7
Arthritis Meds (% taking)	12.2	7.0	13.0	10.3
Head Injury History (%)	11.8	10.5	12.3	10.9
Mobility				
Timed Turn (s)	2.73 (0.93)	2.64 (0.80)	2.99 (0.92)	2.88 (0.82)
Timed Walk (s)	6.27 (1.31)	5.89 (1.06)	6.88 (1.57)	6.25 (1.21)
Lifestyle				
Alcohol Use (%)	88.5	93.9	84.8	85.3
Current Nonsmoker (%)	95.8	96.4	96.4	94.1
Physical Activity	15.82 (4.57)	17.17 (5.75)	14.55 (4.65)	15.44 (6.16)
Novel Cognitive Activity	76.23 (15.84)	84.19 (14.15)	67.12 (16.51)	72.16 (18.14)
Social Visits	5.68 (1.40)	5.08 (1.57)	5.40 (1.44)	5.15 (1.42)
Volunteering	3.81 (2.66)	3.14 (2.53)	3.91 (8.60)	3.16 (2.86)
Genetics				
APOE ε4+ *n (%)*	76 (26.4)	34 (29.8)	43 (31.1)	26 (25.5)
CLU CC *n (%)*	112 (38.9)	24 (21.1)	41 (29.9)	39 (38.2)

Note. Results presented as *Mean (Standard Deviation)* unless otherwise stated. † Self-reported health relative to perfect based on 1 = *very good* to 5 = *very poor.* Abbreviations: *n*, sample size; *APOE*, Apolipoprotein E; *CLU*, Clusterin; ε4+, carrying at least one epsilon 4 allele; C, Cytosine.

Table 4.5. Differences in characteristics between female and male participants.

Factor	Females (*n* = 426)	Males (*n* = 216)	p-value†
Demographics			
Age (years)	70.05 (8.91)	72.10 (8.13)	0.005
Education (years)	14.85 (2.88)	15.94 (3.00)	0.000
Married (%)	47.9	86.6	0.000
Living with Someone (%)	54.5	88.4	0.000
Pet Ownership (%)	28.4	30.6	0.581
Functional Biomarkers			
Pulse Pressure (mm Hg)	51.29 (9.80)	52.92 (9.73)	0.049
Peak Flow (L/min)	372.42 (82.21)	523.54 (106.94)	0.000
Grip Strength (kg/f)	24.24 (4.96)	39.35 (7.64)	0.000
Body Mass Index (kg/m^2)	26.76 (4.32)	26.96 (3.34)	0.551
Health			
Subjective Health*	1.84 (0.75)	1.75 (0.69)	0.103
Depression (CES-D)	8.89 (5.36)	7.86 (4.30)	0.157
Diabetes (% with)	5.9	10.2	0.055
Statins (% taking)	10.1	16.7	0.022
Arthritis Meds (% taking)	12.8	9.1	0.224
Head Injury History (%)	12.0	10.7	0.696
Mobility			
Timed Turn (s)	2.81 (0.93)	2.76 (0.81)	0.434
Timed Walk (s)	6.47 (1.42)	6.01 (1.14)	0.000
Lifestyle			
Alcohol Use (%)	87.3	89.8	0.438
Current Nonsmoker (%)	96.0	95.4	0.683
Physical Activity	15.41 (4.63)	16.35 (6.00)	0.030
Novel Cognitive Activity	73.27 (16.60)	78.48 (17.22)	0.000
Social Visits	5.59 (1.42)	5.11 (1.50)	0.000
Volunteering	3.84 (5.35)	3.15 (2.68)	0.074
Genetic Risk			
APOE ε4+ (%)	27.9	29.8	-
CLU CC (%)	36.0	29.2	-

Note. Results presented as *Mean (Standard Deviation)* unless otherwise stated. * Self-reported health relative to perfect based on 1 = *very good* to 5 = *very poor*. † *P*-values were obtained with one-way analyses of variance and χ^2-tests to compare female and male participants. For all continuous variables, values more than 3 SD above or below the mean were removed as outliers. *P*-values were not reported for χ^2-tests when the expected cell count was < 5. Abbreviations: *n*, sample size; *APOE*, Apolipoprotein E; *CLU*, Clusterin; ε4+, carrying at least one epsilon 4 allele; C, Cytosine.

Table 4.6. Baseline characteristics for resilient and non-resilient female *APOE* ε4 carriers.

Factor	Resilient (n = 72)	Non-resilient (n = 47)	p-value[†]
Demographics			
Age (years)	67.00 (8.09)	74.21 (8.05)	0.000
Education (years)	15.43 (2.70)	14.35 (2.21)	0.027
Married (%)	52.6	37.2	0.093
Living with Someone (%)	56.6	46.5	0.161
Pet Ownership (%)	28.9	32.6	0.490
Functional Biomarkers			
Pulse Pressure (mm Hg)	50.17 (10.03)	53.87 (10.41)	0.060
Peak Flow (L/min)	402.16 (62.45)	369.88 (83.37)	0.021
Grip Strength (kg/f)	25.37 (4.60)	23.52 (4.77)	0.044
Body Mass Index (kg/m^2)	26.08 (4.07)	26.26 (4.05)	0.818
Health			
Subjective Health*	1.63 (0.67)	1.81 (0.82)	0.785
Depression (CES-D)	8.36 (4.43)	10.17 (5.99)	0.064
Diabetes (% with)	2.6	2.3	NA
Statins (% taking)	13.2	16.3	0.416
Arthritis Meds (% taking)	19.4	11.6	0.204
Head Injury History (%)	11.8	7.0	NA
Mobility			
Timed Turn (s)	2.60 (0.87)	2.97 (0.73)	0.021
Timed Walk (s)	6.11 (1.23)	6.89 (1.46)	0.003
Lifestyle			
Alcohol Use (%)	86.8	86.0	0.555
Current Nonsmoker (%)	96.1	95.3	NA
Physical Activity	15.97 (4.19)	15.33 (4.77)	0.444
Novel Cognitive Activity	77.24 (13.41)	69.44 (17.48)	0.008
Social Visits	5.71 (1.43)	5.33 (1.46)	0.170
Volunteering	3.83 (2.63)	3.37 (2.50)	0.359

Note. Results presented as *Mean (Standard Deviation)* unless otherwise stated. * Self-reported health relative to perfect based on 1 = *very good* to 5 = *very poor*. [†] *P*-values were obtained with one-way analyses of variance and χ^2-tests to compare resilient and non-resilient participants. For all continuous variables, values more than 3 SD above or below the mean were removed as outliers. *P*-values were not reported for χ^2-tests when the expected cell count was < 5. Abbreviations: *n*, sample size; NA, not available, cell count too small.

Table 4.7. Baseline characteristics for resilient and non-resilient male *APOE* ε4 carriers.

Factor	Resilient (n = 34)	Non-resilient (n = 26)	p-value[†]
Demographics			
Age (years)	67.59 (6.66)	74.12 (6.38)	0.000
Education (years)	17.85 (2.68)	14.08 (2.94)	0.000
Married (%)	79.4	96.2	NA
Living with Someone (%)	85.3	96.2	NA
Pets Ownership (%)	35.3	38.5	0.506
Functional Biomarkers			
Pulse Pressure (mm Hg)	51.43 (10.44)	55.24 (10.18)	0.162
Peak Flow (L/min)	542.06 (118.28)	507.80 (110.06)	0.262
Grip Strength (kg/f)	41.11 (7.12)	36.56 (6.94)	0.019
Body Mass Index (kg/m^2)	27.13 (2.96)	26.75 (2.57)	0.612
Health			
Subjective Health*	1.56 (0.61)	1.65 (0.80)	0.603
Depression (CES-D)	6.88 (3.25)	9.15 (5.30)	0.047
Diabetes (% with)	8.8	11.5	NA
Statins (% taking)	8.8	15.4	NA
Arthritis Meds (% taking)	8.8	7.7	NA
Head Injury History (%)	5.9	3.8	NA
Mobility			
Timed Turn (s)	2.67 (0.86)	2.88 (0.91)	0.356
Timed Walk (s)	5.97 (1.04)	6.31 (1.12)	0.222
Lifestyle			
Alcohol Use (%)	94.1	76.9	NA
Current nonsmoker (%)	94.1	92.3	NA
Physical Activity	17.71 (5.93)	15.96 (5.93)	0.264
Novel Cognitive Activity	86.18 (11.97)	74.04 (19.98)	0.005
Social Visits	5.03 (1.59)	5.42 (1.42)	0.323
Volunteering	2.71 (2.46)	2.46 (2.96)	0.728

Note. Results presented as *Mean (Standard Deviation)* unless otherwise stated.
* Self-reported health relative to perfect based on 1 = *very good* to 5 = *very poor*.
[†] *P*-values were obtained with one-way analyses of variance and χ^2-tests to compare resilient and non-resilient participants. For all continuous variables, values more than 3 SD above or below the mean were removed as outliers. *P*-values were not reported for χ^2-tests when the expected cell count was < 5. NA = not available, cell count too small. Abbreviations: *n*, sample size; NA, not available, cell count too small.

Table 4.8. Baseline characteristics for resilient and non-resilient female *CLU* C homozygotes.

Factor	Resilient (n = 112)	Non-resilient (n = 41)	p-value[†]
Demographics			
Age (years)	68.68 (8.86)	73.34 (7.60)	0.003
Education (years)	15.91 (2.81)	12.92 (2.39)	0.000
Married (%)	47.3	41.5	0.323
Living with Someone (%)	53.2	43.9	0.203
Pet Ownership (%)	29.5	19.5	0.171
Functional Biomarkers			
Pulse Pressure (mm Hg)	50.79 (9.69)	55.95 (8.57)	0.004
Peak Flow (L/min)	372.80 (80.80)	363.65 (76.69)	0.546
Grip Strength (kg/f)	25.08 (5.18)	21.74 (4.98)	0.001
Body Mass Index (kg/m^2)	26.61 (4.16)	27.22 (4.13)	0.429
Health			
Subjective Health*	1.82 (0.67)	2.22 (0.85)	0.006
Depression (CES-D)	8.46 (5.21)	9.48 (6.11)	0.312
Diabetes (% with)	4.5	12.2	NA
Statins (% taking)	8.0	14.6	NA
Arthritis Meds (% taking)	9.8	17.1	0.170
Head Injury History (%)	14.3	9.8	0.593
Mobility			
Timed Turn (s)	2.68 (0.84)	3.06 (0.89)	0.017
Timed Walk (s)	6.28 (1.29)	7.06 (1.71)	0.004
Lifestyle			
Alcohol Use (%)	88.4	70.7	0.011
Current Nonsmoker (%)	97.3	97.6	NA
Physical Activity	15.88 (4.38)	14.49 (4.84)	0.092
Novel Cognitive Activity	76.18 (15.81)	67.00 (16.04)	0.002
Social Visits	5.92 (1.31)	5.24 (1.36)	0.006
Volunteering	3.71 (2.63)	3.54 (2.68)	0.718

Note. Results presented as *Mean (Standard Deviation)* unless otherwise stated.
* Self-reported health relative to perfect based on 1 = *very good* to 5 = *very poor*.
[†] *P*-values were obtained with one-way analyses of variance and χ^2-tests to compare resilient and non-resilient participants. For all continuous variables, values more than 3 SD above or below the mean were removed as outliers. *P*-values were not reported for χ^2-tests when the expected cell count was < 5. NA = not available, cell count too small. Abbreviations: *n*, sample size; NA, not available, cell count too small.

Table 4.9. Baseline characteristics for resilient and non-resilient male *CLU* C homozygotes.

Factor	Resilient (n = 24)	Non-resilient (n = 39)	p-value[†]
Demographics			
Age (years)	67.21 (7.44)	75.44 (7.02)	0.000
Education (years)	16.50 (1.74)	14.90 (2.78)	0.014
Married (%)	83.3	87.2	NA
Living with Someone (%)	87.0	87.2	NA
Pet Ownership (%)	33.3	20.5	0.200
Functional Biomarkers			
Pulse Pressure (mm Hg)	48.20 (9.31)	54.48 (10.02)	0.020
Peak Flow (L/min)	559.37 (115.68)	519.23 (106.13)	0.164
Grip Strength (kg/f)	43.81 (7.63)	37.31 (6.56)	0.001
Body Mass Index (kg/m^2)	26.06 (3.07)	27.03 (3.69)	0.295
Health			
Subjective Health*	1.58 (0.65)	1.74 (0.64)	0.341
Depression (CES-D)	7.38 (2.41)	10.32 (5.56)	0.017
Diabetes (% with)	8.3	17.9	0.251
Statins (% taking)	20.8	17.9	NA
Arthritis Meds (% taking)	5.6	11.1	NA
Head Injury History (%)	16.7	10.3	NA
Mobility			
Timed Turn (s)	2.74 (0.84)	2.97 (0.86)	0.300
Timed Walk (s)	5.70 (1.18)	6.21 (1.21)	0.106
Lifestyle			
Alcohol Use (%)	95.8	92.3	NA
Current Nonsmoker (%)	95.8	92.3	NA
Physical Activity	15.21 (5.24)	15.92 (5.54)	0.614
Novel Cognitive Activity	80.96 (11.96)	77.89 (19.40)	0.490
Social Visits	4.42 (1.59)	5.13 (1.45)	0.073
Volunteering	2.46 (2.50)	3.56 (2.92)	0.129

Note. Results presented as *Mean (Standard Deviation)* unless otherwise stated. * Self-reported health relative to perfect based on 1 = *very good* to 5 = *very poor.* [†] *P*-values were obtained with one-way analyses of variance and χ^2-tests to compare resilient and non-resilient participants. For all continuous variables, values more than 3 SD above or below the mean were removed as outliers. *P*-values were not reported for χ^2-tests when the expected cell count was < 5. NA = not available, cell count too small. Abbreviations: *n*, sample size; NA, not available, cell count too small.

Table 4.10. Baseline characteristics for resilient and non-resilient females with a high genetic risk score.

Factor	Resilient (n = 68)	Non-resilient (n = 31)	p-value[†]
Demographics			
Age (years)	67.22 (8.41)	73.65 (8.28)	0.001
Education (years)	15.41 (2.75)	14.26 (2.18)	0.042
Married (%)	50.0	28.7	0.244
Living with Someone (%)	54.4	38.7	0.137
Pet Ownership (%)	27.9	25.8	0.551
Functional Biomarkers			
Pulse Pressure (mm Hg)	50.02 (10.16)	54.28 (11.08)	0.063
Peak Flow (L/min)	402.16 (62.78)	370.65 (85.54)	0.043
Grip Strength (kg/f)	25.27 (4.57)	23.53 (4.33)	0.089
Body Mass Index (kg/m^2)	25.53 (3.65)	26.52 (4.16)	0.241
Health			
Subjective Health*	1.57 (0.63)	1.90 (0.91)	0.039
Depression (CES-D)	8.57 (4.58)	10.55 (6.12)	0.077
Diabetes (% with)	2.9	3.2	NA
Statins (% taking)	13.2	16.1	NA
Arthritis Meds (% taking)	16.9	9.7	NA
Head Injury History (%)	7.4	3.2	NA
Mobility			
Timed Turn (s)	2.64 (0.89)	3.07 (0.74)	0.024
Timed Walk (s)	6.15 (1.27)	6.91 (1.57)	0.015
Lifestyle			
Alcohol Use (%)	85.3	80.6	NA
Current Nonsmoker (%)	95.6	96.8	NA
Physical Activity	16.03 (4.33)	15.29 (5.24)	0.465
Novel Cognitive Activity	76.96 (13.73)	67.32 (15.35)	0.002
Social Visits	5.72 (1.44)	5.26 (1.46)	0.149
Volunteering	3.78 (2.62)	3.58 (2.41)	0.726

Note. Results presented as *Mean (Standard Deviation)* unless otherwise stated.
* Self-reported health relative to perfect based on 1 = *very good* to 5 = *very poor*.
[†] *P*-values were obtained with one-way analyses of variance and χ^2-tests to compare resilient and non-resilient participants. For all continuous variables, values more than 3 SD above or below the mean were removed as outliers. *P*-values were not reported for χ^2-tests when the expected cell count was < 5.
Abbreviations: *n*, sample size; NA, not available, cell count too small.

Table 4.11. Baseline characteristics for resilient and non-resilient males with a high genetic risk score.

Factor	Resilient (n = 27)	Non-resilient (n = 22)	p-value[†]
Demographics			
Age (years)	68.00 (6.98)	73.68 (6.79)	0.006
Education (years)	17.85 (2.64)	13.82 (2.48)	0.000
Married (%)	77.8	95.5	NA
Living with Someone (%)	85.2	95.5	NA
Pet Ownership (%)	40.7	45.5	0.779
Functional Biomarkers			
Pulse Pressure (mm Hg)	52.94 (11.09)	54.82 (9.08)	0.526
Peak Flow (L/min)	564.07 (105.03)	487.62 (101.34)	0.015
Grip Strength (kg/f)	41.95 (7.64)	36.98 (7.22)	0.029
Body Mass Index (kg/m^2)	26.99 (2.96)	27.00 (2.69)	0.984
Health			
Subjective Health*	1.52 (0.51)	1.73 (0.83)	0.284
Depression (CES-D)	8.44 (3.27)	8.52 (5.28)	0.949
Diabetes (% with)	11.1	13.6	NA
Statins (% taking)	11.1	13.6	NA
Arthritis Meds (% taking)	14.3	9.5	NA
Head Injury History (%)	7.4	4.5	NA
Mobility			
Timed Turn (s)	2.73 (0.87)	2.99 (0.94)	0.323
Timed Walk (s)	5.99 (1.00)	6.38 (1.21)	0.231
Lifestyle			
Alcohol Use (%)	92.6	72.7	NA
Current Nonsmoker (%)	96.3	90.9	NA
Physical Activity	17.78 (6.17)	15.36 (6.23)	0.181
Novel Cognitive Activity	84.81 (11.68)	73.77 (21.01)	0.026
Social Visits	4.81 (1.64)	5.41 (1.53)	0.201
Volunteering	2.63 (2.44)	2.64 (3.11)	0.993

Note. Results presented as *Mean (Standard Deviation)* unless otherwise stated.
* Self-reported health relative to perfect based on 1 = *very good* to 5 = *very poor*.
[†] *P*-values were obtained with one-way analyses of variance and χ^2-tests to compare resilient and non-resilient participants. For all continuous variables, values more than 3 SD above or below the mean were removed as outliers. *P*-values were not reported for χ^2-tests when the expected cell count was < 5.
Abbreviations: *n*, sample size; NA, not available, cell count too small.

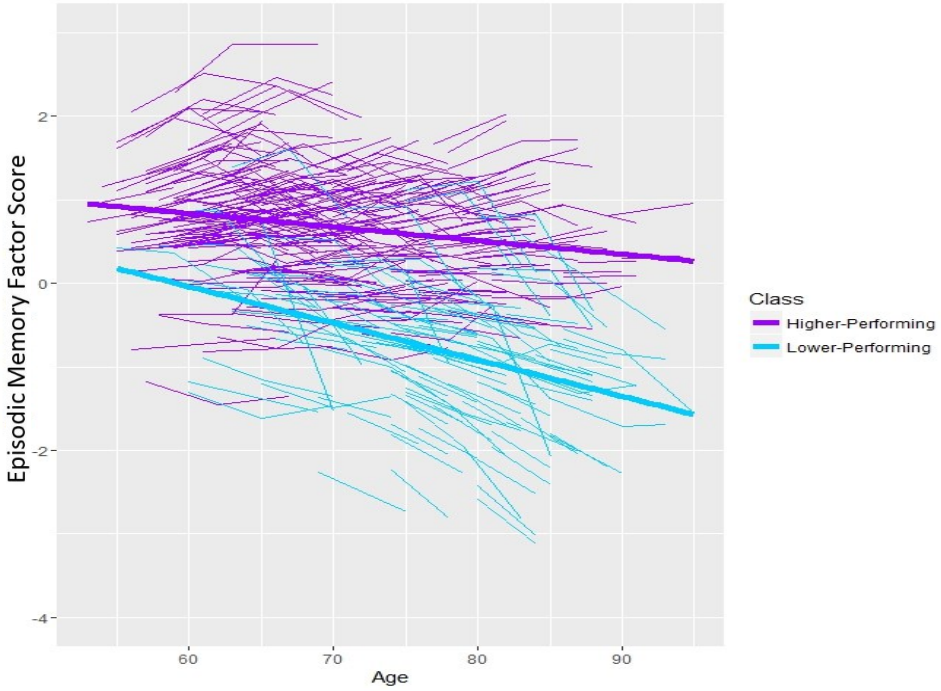


Figure 4.1. Female episodic memory trajectories differentiated into "higher-performing" and "lower-performing" with growth mixture modelling. Only participants with at least two waves of episodic memory data were included.

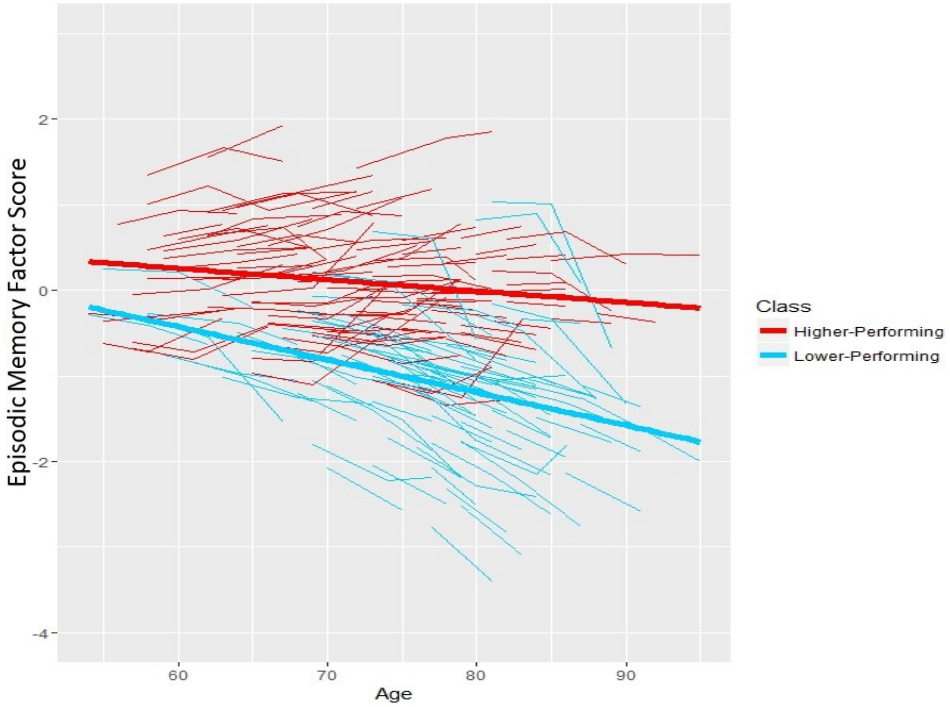


Figure 4.2. Male episodic memory trajectories differentiated into "higher-performing" and "lower-performing" with growth mixture modelling. Only participants with at least two waves of episodic memory data were included.

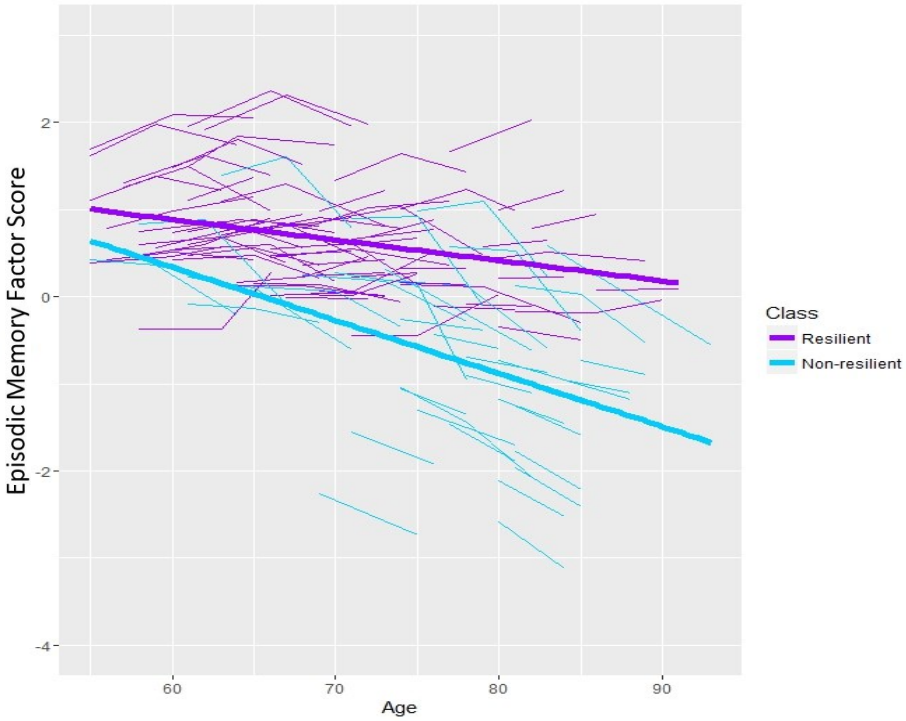


Figure 4.3. Episodic memory trajectories for females resilient and non-resilient to the *APOE* ε4 allele. Only participants with at least two waves of episodic memory data were included.

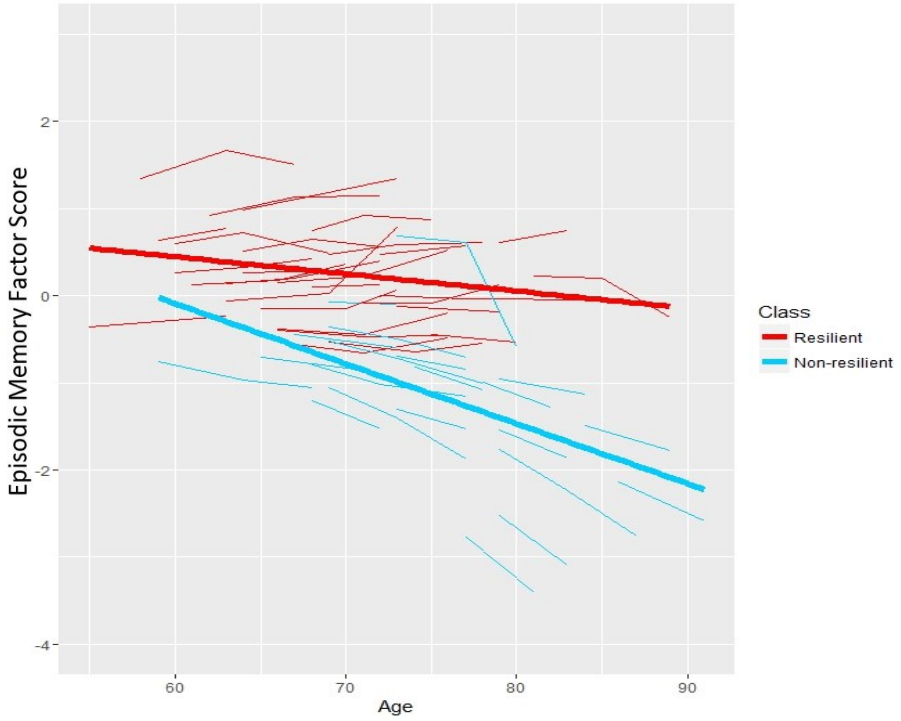


Figure 4.4. Episodic memory trajectories for males resilient and non-resilient to the *APOE* ε4 allele. Only participants with at least two waves of episodic memory data were included.

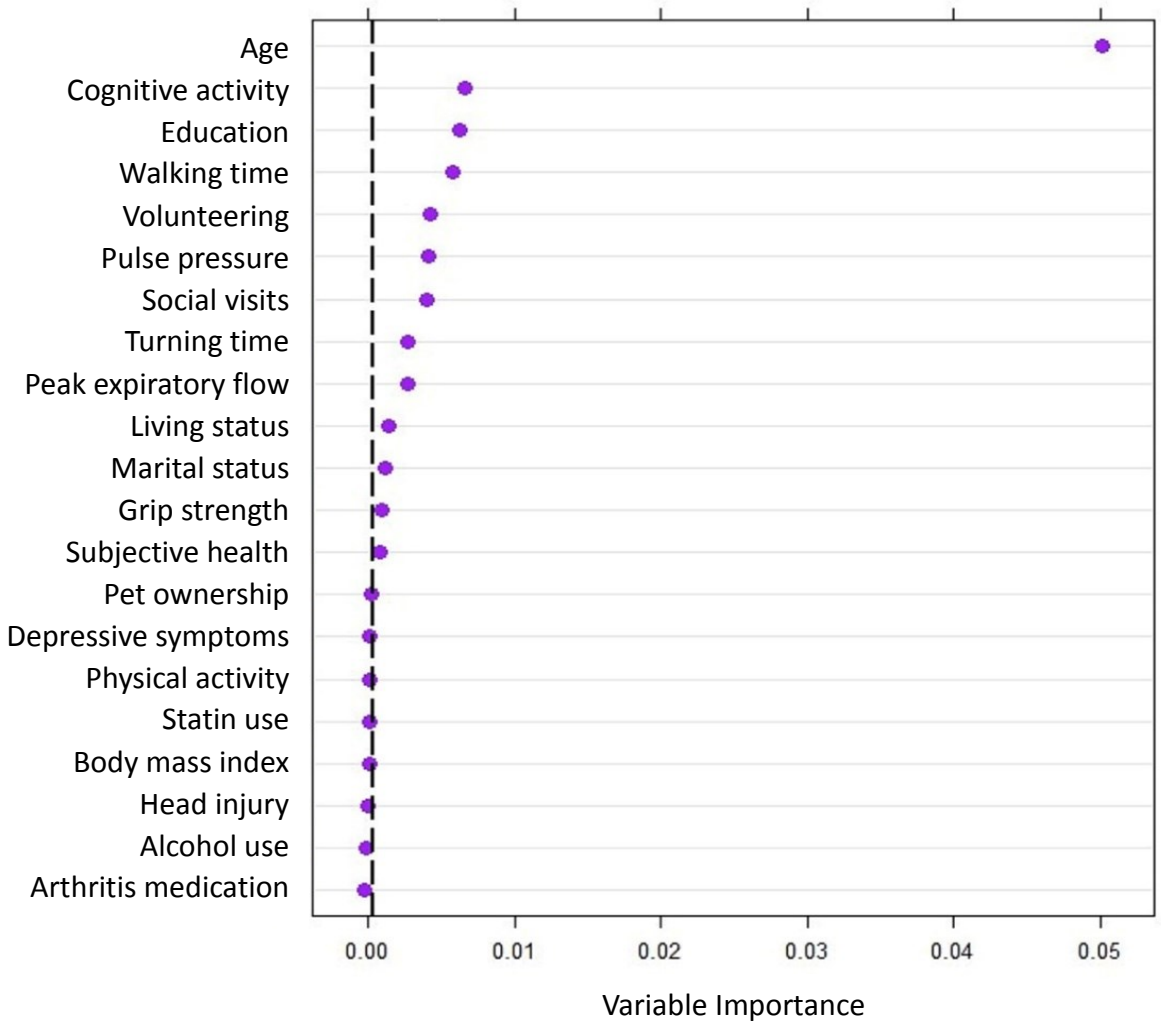


Figure 4.5. Random forest analysis results to identify the strongest predictors of episodic memory resilience in female *APOE* ε4 carriers. Dotted black line represents cut-off for variable importance. Model statistics: $N = 153$ (76 resilient, 77 non-resilient), *Ntree* = 5000, *Mtry* = 5, C = 0.82.

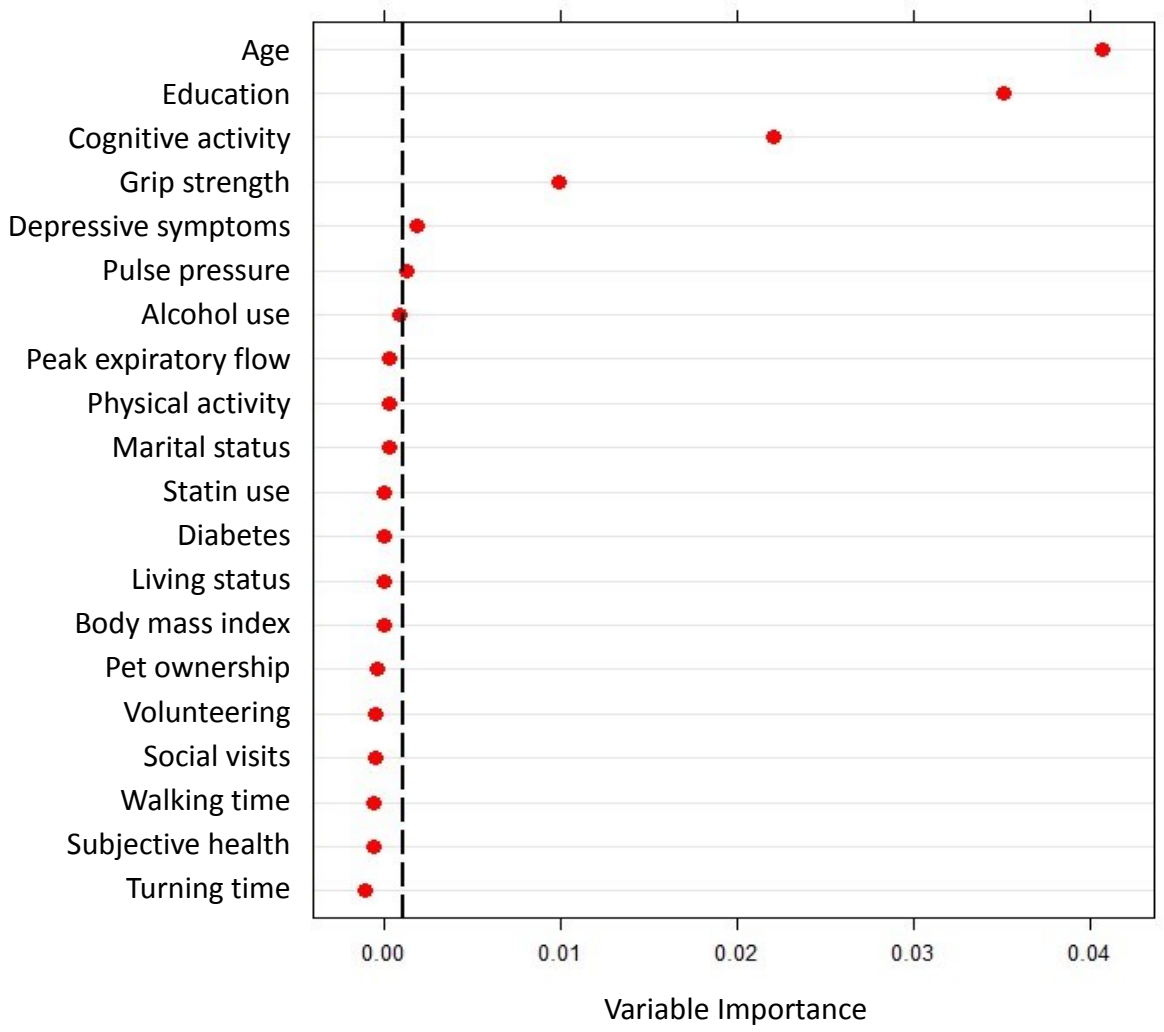


Figure 4.6. Random forest analysis results to identify the strongest predictors of episodic memory resilience in male *APOE* ε4 carriers. Dotted black line represents cut-off for variable importance. Model statistics: *N* = 65 (33 resilient, 32 non-resilient), *Ntree* = 5000, *Mtry* = 5, C = 0.78.

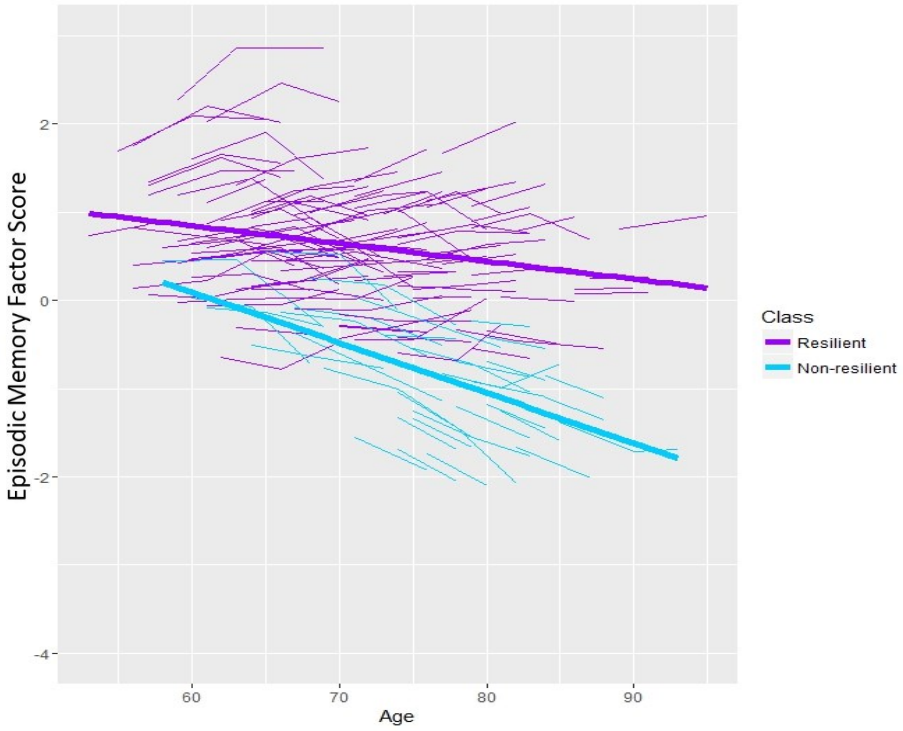


Figure 4.7. Episodic memory trajectories for females resilient and non-resilient to the *CLU* CC genotype. Only participants with at least two waves of episodic memory data were included.

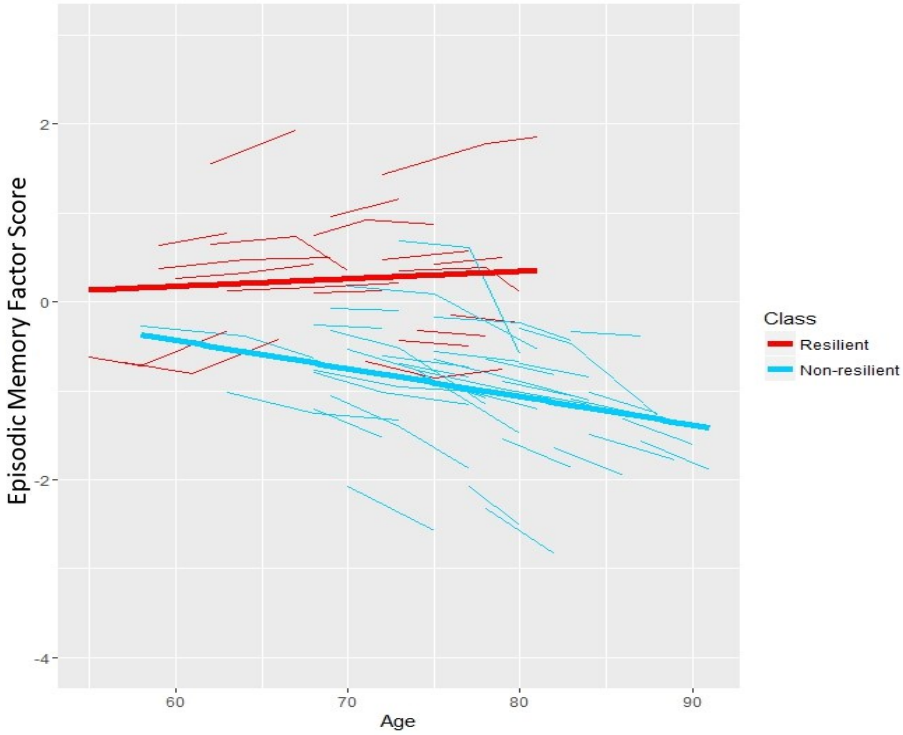


Figure 4.8. Episodic memory trajectories for males resilient and non-resilient to the *CLU* CC genotype. Only participants with at least two waves of episodic memory data were included.

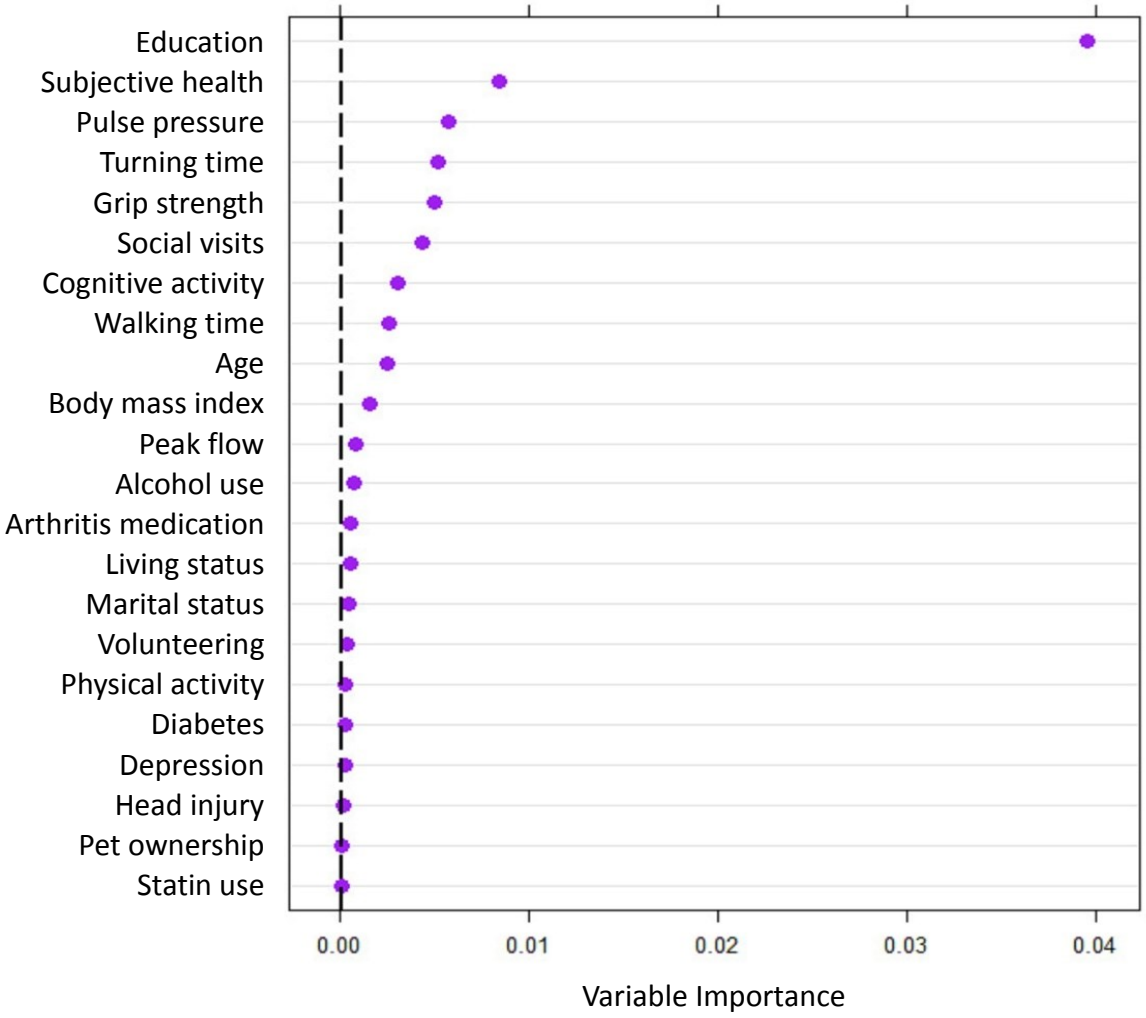


Figure 4.9. Random forest analysis results to identify the strongest predictors of episodic memory resilience in female *CLU* C homozygotes. Dotted black line represents cut-off for variable importance. Model statistics: $N = 235$ (112 resilient, 123 non-resilient), *Ntree* = 5000, *Mtry* = 5, C = 0.91.

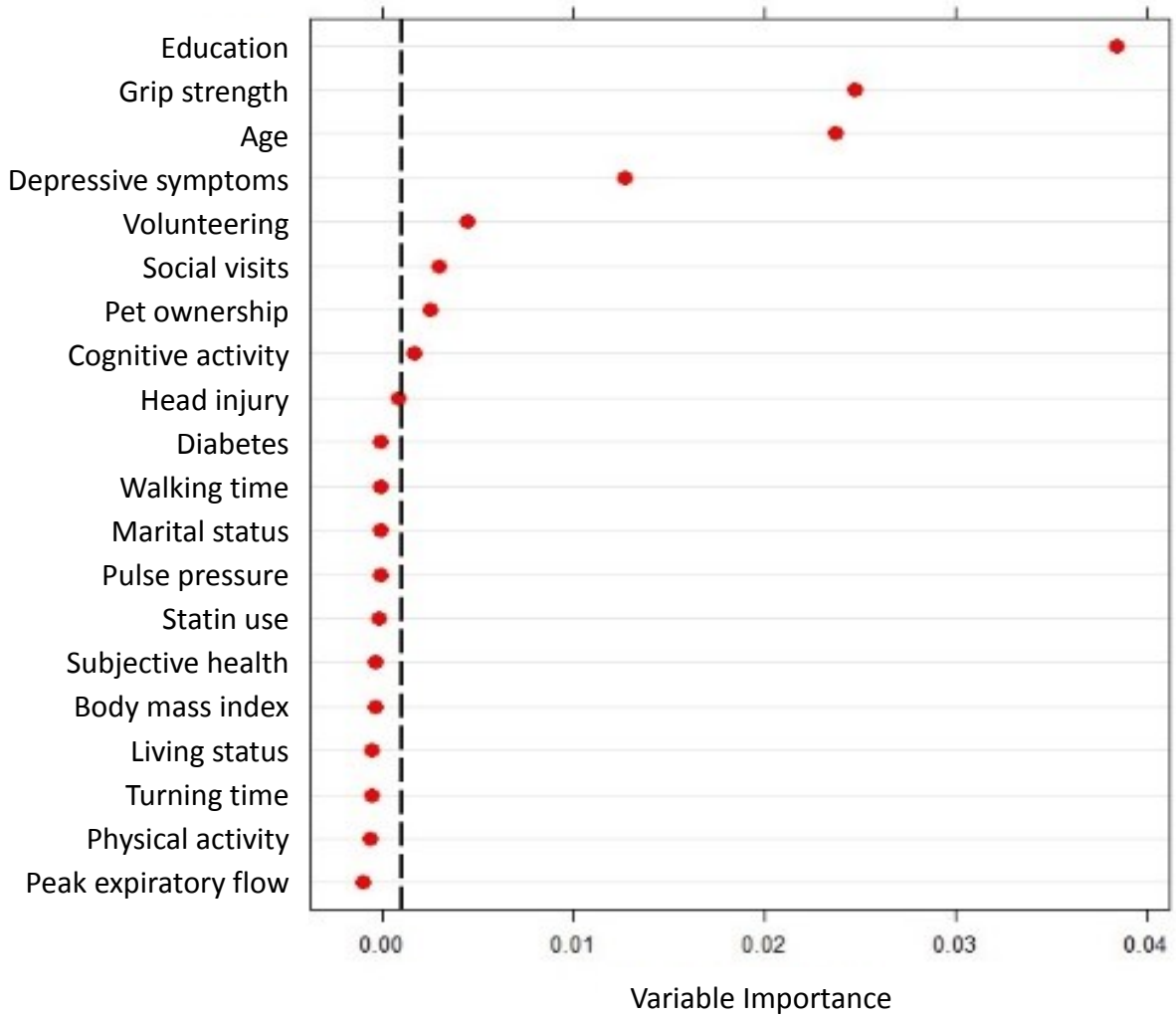


Figure 4.10. Random forest analysis results to identify the strongest predictors of episodic memory resilience in male *CLU* C homozygotes. Dotted black line represents cut-off for variable importance. Model statistics: *N* = 72 (36 resilient, 36 non-resilient), *Ntree* = 5000, *Mtry* = 5, C = 0.77.

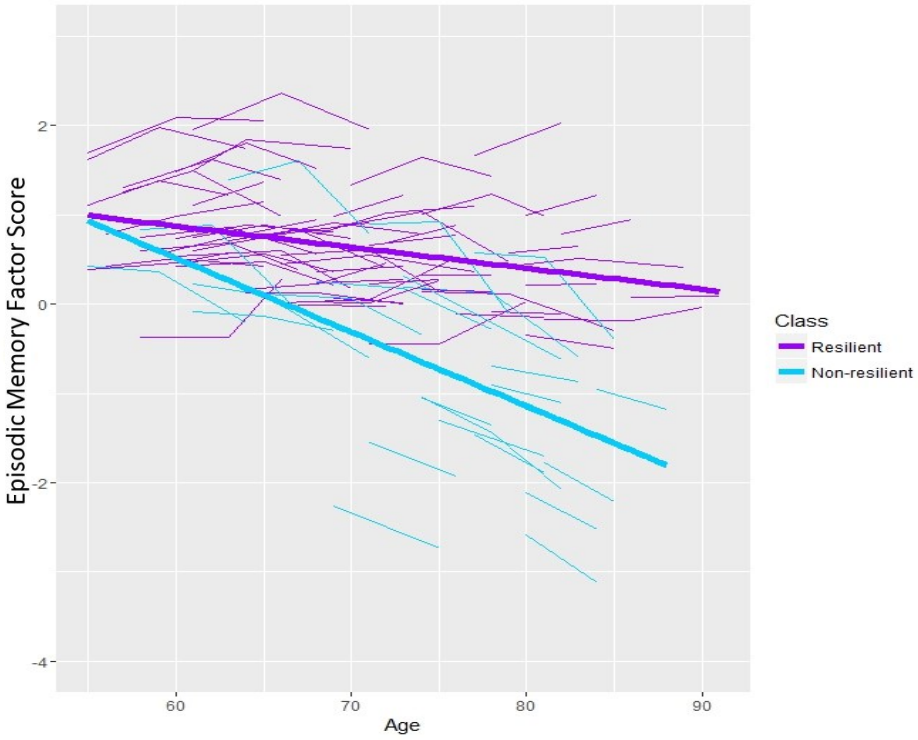


Figure 4.11. Episodic memory trajectories for females resilient and non-resilient to a high genetic risk score. Only participants with at least two waves of episodic memory data were included.

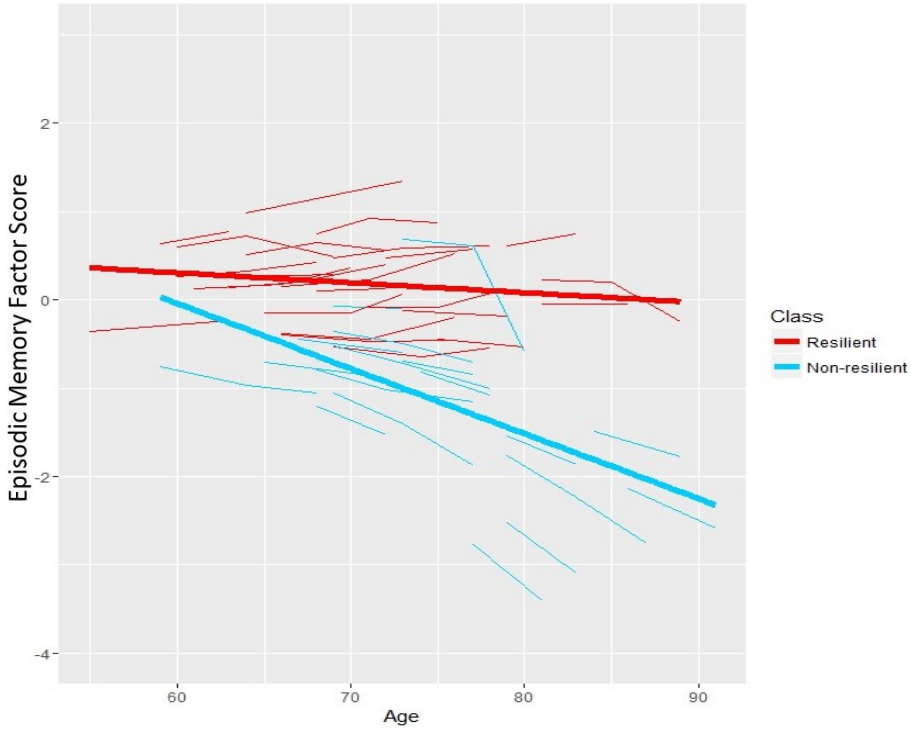


Figure 4.12. Episodic memory trajectories for males resilient and non-resilient to a high genetic risk score. Only participants with at least two waves of episodic memory data were included.

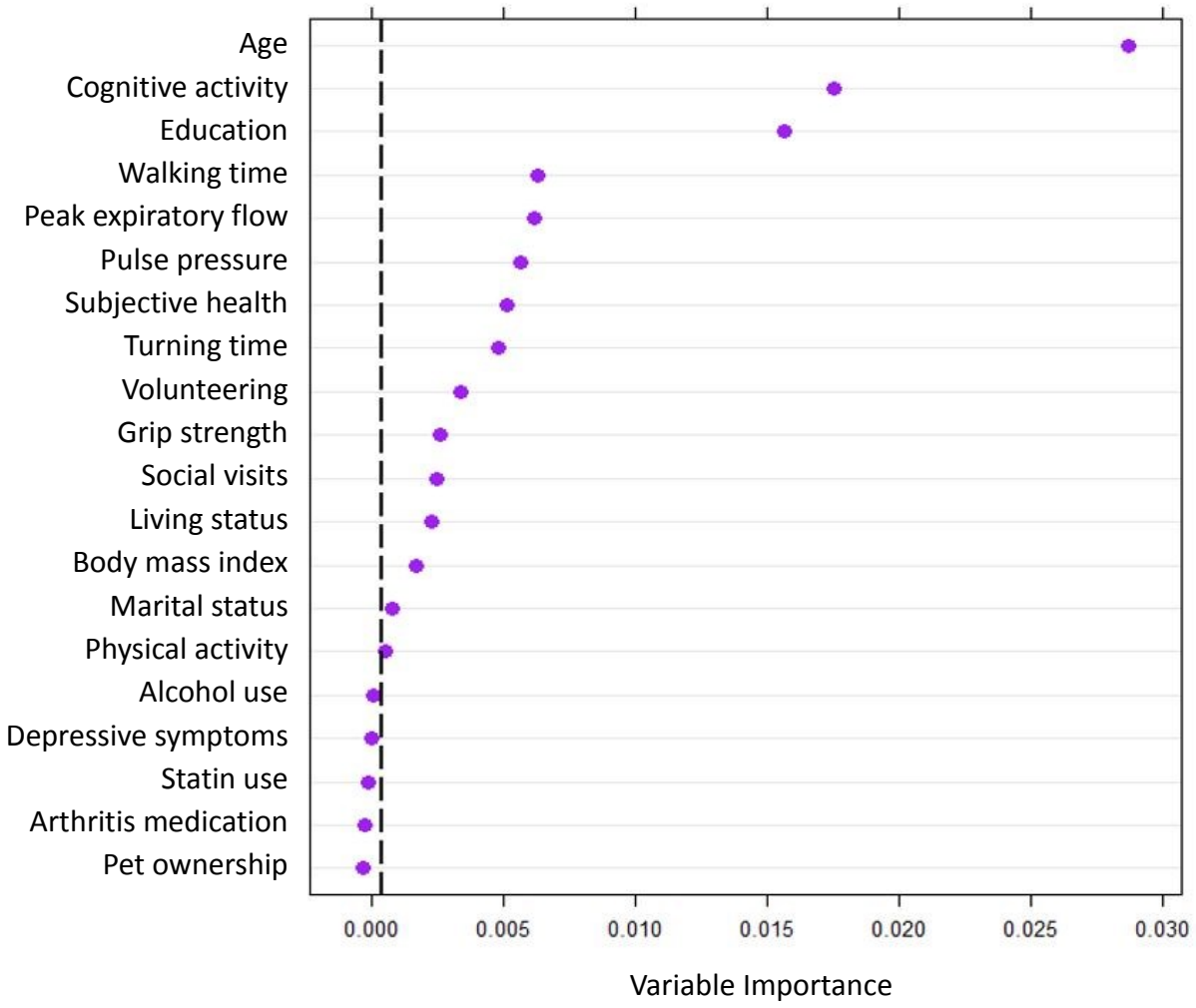


Figure 4.13. Random forest analysis results to identify the strongest predictors of episodic memory resilience in female participants with a high genetic risk score. Dotted black line represents cut-off for variable importance. Model statistics: *N* = 124 (62 resilient, 62 non-resilient), *Ntree* = 5000, *Mtry* = 5, C = 0.80.

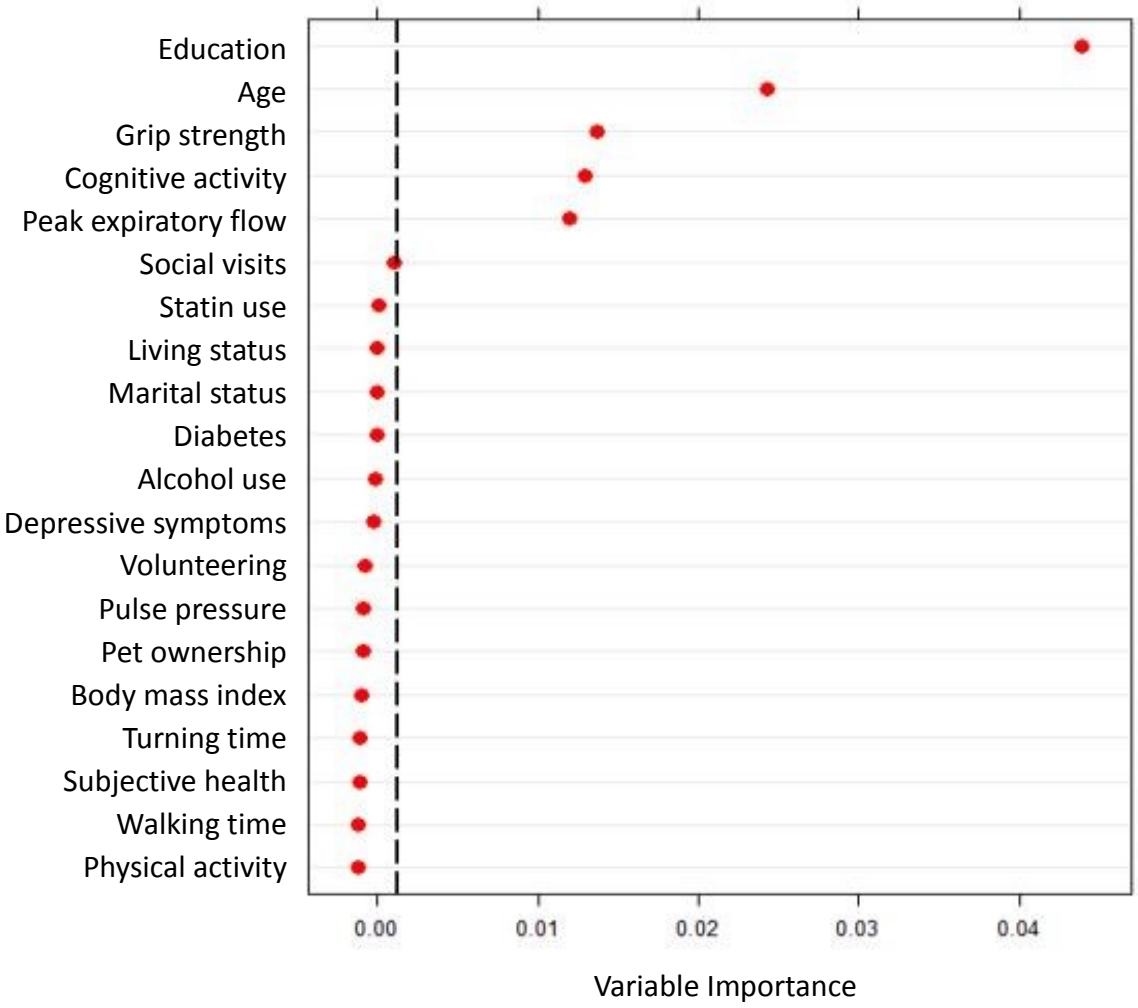


Figure 4.14. Random forest analysis results to identify the strongest predictors of episodic memory resilience in male participants with a high genetic risk score. Dotted black line represents cut-off for variable importance. Model statistics: *N* = 124 (62 resilient, 62 non-resilient), *Ntree* = 5000, *Mtry* = 5, C = 0.78.

	F ε4	M ε4	F CC	M CC	F GRS	M GRS
Age						
Education						
Marital status						
Living status						
Pet ownership						
Pulse pressure						
Peak expiratory flow						
Grip strength						
Body mass index						
Subjective health						
Depressive symptoms						
Diabetes						
Statins						
Arthritis medication						
Head injury history						
Timed turn						
Timed walk						
Alcohol use						
Physical activity						
Cognitive activity						
Social visits						
Volunteering						

Important across sex, genetic risk

Sex-specific, genetically robust

Sex-specific, not genetically robust

Not included (low prevalence)

Not important

Figure 4.15. Summary of predictors of resilience by genetic variant and sex. Blue boxes indicate the factor was an important predictor of resilience across sex and genetic risk. Purple boxes indicate the factor was a sex-specific and genetically robust predictor of resilience. Green boxes indicate the factor an important predictor of resilience but not genetically robust. Grey boxes represent factors not included in analyses due to low prevalence. White boxes represent factors that were not important predictors of resilience. Abbreviations: F, female; M, male; ε4, carries of the *APOE* ε4 allele; CC, carriers of the *CLU* CC genotype; GRS , high genetic risk score; PP, pulse pressure; PEF, peak expiratory flow; GS, grip strength; BMI, body mass index.

Chapter 5 – Discussion

The overall purpose of this study was to examine predictors of memory resilience to AD genetic risk. We had three main research goals. Regarding research goal 1, we examined whether multiple longitudinal memory performance phenotypes could be differentiated for females and males based on their EM latent variable performance and nine-year trajectory. Our single-factor EM latent variable was unified and stable across all three waves (as it exhibited configural, metric and partial scalar invariance). To distinguish memory performance phenotypes, we used growth mixture modelling. As expected, we differentiated two classes of memory trajectories for females and males: a "higher-performing" class, characterized by better baseline performance and more favorable trajectory and a "lower-performing" class, characterized by worse baseline performance and more steeply declining slope. Our results support the idea that, although memory performance declines in normal aging (an effect which may be enhanced in carriers of AD genetic risk), substantial interindividual variability exists within a large cohort of older adults. We note that, of our three specified genetic risk factors, only the *APOE* ε4 allele was a risk for steeper memory decline, specifically in females. Although somewhat surprising, it is not uncommon for established genetic risk variants to demonstrate insignificant effects on cognition independently (McFall et al., 2016; McFall et al., 2015). We felt confident in our definition of resilience to AD genetic risk and moved forward with the planned analyses.

Once the memory trajectories were distinguished we defined memory resilience as being within the higher-performing class despite carrying specified AD genetic risk (i.e., the *APOE* ε4 allele, the *CLU* CC genotype, or a high GRS). Non-resilient participants carried AD genetic risk but were in the lower-performing class. For research goals 2 and 3, we tested 22 predictors of resilience from five relevant domains. Specifically, we were interested in which predictors (and

predictor profiles) of resilience would emerge as sex-similar, sex-specific, and genetically robust. To accomplish these goals, we used random forest analysis (RFA). Our resilient participants had a more favorable profile of factors from multiple AD risk domains. However, the specific predictor profiles varied by sex. We found several important similarities in predictors of resilience but also (a) numerous factors from all five domains that differentially predicted resilience in females and (b) relatively few unique factors from the demographic and health domains that predicted resilience in males. For both sexes, most of the factors tested were genetically robust predictors across *APOE*- and *CLU*-based resilience. The majority of the genetically robust predictor profiles were also matched, by informal comparison, in GRS-based resilience. In the subsequent sections, we discuss our RFA results by domain and assess their implications more broadly.

Altogether, our findings suggest that diverse AD risk and protective factors predict memory resilience in adults with AD genetic risk. However, the specific predictor profiles exhibit similarities and differences between males and females. Our results contribute to, and enhance the, findings of previous research by (a) specifically assessing EM with a robust latent variable, (b) investigating sex effects in predictors of resilience, and (c) testing 22 documented non-genetic AD risk and protective factors. Modifiable factors offer targets for sex-specific, multifactorial interventions to promote healthy brain aging, sustain functional independence, and delay cognitive impairment in adults with AD genetic risk.

5.1. Demographic Factors

Within the demographic domain, younger age emerged as (a) an important predictor of resilience for both sexes and (b) genetically robust. Our design permitted a strong test of chronological age predictions within an older adult sample spanning a 40-year band of aging.

This effect was likely due, in part, to the numerous aging-related brain changes that affect cognition progressively even in non-demented older adults. For example, brain volume decreases with age including within areas essential to memory performance such as the hippocampus (Bherer, Erickson, & Liu-Ambrose, 2013). Non-demented older adults exhibit greater AD pathology with age which can also negatively impact memory ability; this effect is further exacerbated in *APOE* ε4 carriers (Chetelat & Fouquet, 2013). However, our age results differ from those of a recent study in which older age was an important predictor of global cognitive resilience to the *APOE* ε4 allele in white older adults (Kaup et al., 2015). Conceivably, EM trajectories may be more systematically distributed and sensitive to subtle age changes. We underscore the importance of age as a predictor in all of our models but because it is unmodifiable factor we focus on other, potentially modifiable, predictors of resilience. Furthermore, we note that by including age in all of our models (despite our primary interest in modifiable predictors of resilience), we thereby accounted for its effect on other variables (e.g., grip strength) that may have emerged as more important simply due to age differences between resilient and non-resilient groups.

Cognitive resilience (to the *APOE* ε4 allele; in black and white older adults) and memory resilience (to the ε4 allele, CC genotype, and a high GRS; in females and males) were both strongly predicted by higher educational attainment. Education may promote resilience to *APOE* and *CLU* risk alleles and their combined GRS by enhancing cognitive reserve (Josefsson et al., 2012; Schneeweis, Skirbekk, & Winter-Ebmer, 2014), thereby protecting against memory decline by counteracting negative effects of genetic risk factors (Arenaza-Urquijo et al., 2015). Although level of education is not generally modified after age 55, our results further support

that (a) cognitive reserve likely play a major role in resilient phenotypes and (b) we should encourage young and mid-life adults to pursue further training or education.

Two related demographic factors—being married and living with someone—were genetically robust predictors of resilience in females. In previous studies, above-average global cognition and EM ability have both been associated with living with someone (Josefsson et al., 2012; Yaffe et al., 2009). Close social ties have been shown in multiple studies to protect against dementia and promote cognitive maintenance, however the exact mechanisms are unclear (Pillai & Verghese, 2009). These results coincide with the social lifestyle factors (i.e., volunteering and social visits) which also emerged as important, genetically robust predictors of resilience for females in our study. We note, however, that cognitive resilience to the *APOE* ε4 allele was not predicted by either living status or marital status in mixed-sex analyses stratified by race (Kaup et al., 2015). The differing results could be a result of our sex-stratification or because living status may have more of an effect on memory resilience. Neither factor predicted resilience in males with any form of AD genetic risk. It is possible that such measures may be more salient for females because, on average, they outlive males (Kannel, 2002).

Finally, pet ownership predicted *CLU*-based memory resilience in males. This effect was not genetically robust so likely not a strong candidate for future investigation. However, owning a pet may encourage healthy lifestyle activities or reduce stress so may warrant future study in other areas (Arhant-Sudhir, Arhant-Sudhir, & Sudhir, 2011; Cherniack & Cherniack, 2014).

5.2. Functional Biomarkers

We found that stronger grip was an important predictor of resilience across both sexes and within all genetic risk groups. Furthermore, GS often emerged as relatively more important than many other factors. GS is considered one of the best measures of age-related loss of muscle

mass (Cruz-Jentoft, Landi, Topinkova, & Michel, 2010). Sarcopenia and poor grip strength have been associated with cognitive impairment and decline, frailty, disability, and mortality in older adults (den Ouden, Schuurmans, Mueller-Schotte, & van der Schouw, 2013; Hsu et al., 2014; Legrand et al., 2014; Sternäng et al., 2015). GS is a key marker of frailty, more so than chronological age (Bohannon, 2008; Syddall, Cooper, Martin, Briggs, & Aihie Sayer, 2003), and its effects on cognition and health outcomes can be differentially influenced by genetic and environmental factors (Petersen et al., 2016). Frailty (as measured with grip strength, timed walk, BMI, and fatigue) is associated with an increased risk of cognitive decline and AD (Buchman, Boyle, Wilson, Tang, & Bennett, 2007). That our GS results were general across sex and genetic risk underscores the importance of staying physically healthy and avoiding frailty in old age. Overall, the relationship between memory and fine muscle strength suggests that (a) grip strength is a useful and simple biomarker of cognitive performance or change and (b) interventions involving strength-training may be associated with sustained memory performance in at-risk older adults, possibly by reducing frailty.

The remaining functional biomarkers emerged as important predictors of resilience almost exclusively in females: lower PP and higher PEF were genetically robust predictors of resilience whereas lower BMI was specific to *CLU*- and GRS-based resilience. There was one effect in males: PEF was a predictor of resilience in males with a high GRS, but not with *APOE* or *CLU* risk independently.

Our PP results support that better vascular health has positive effect on memory and cognition, albeit specifically in females. For example, poor vascular health (i.e., higher PP) can increase the risk of (a) EM decrements in aging *APOE* ε4 carriers (McFall et al., 2015) and (b) cognitive impairment in non-demented older females (Yasar, Ko, Nothelle, Mielke, & Carlson,

2011). Interestingly, hypertension was not an important predictor of cognitive resilience in the resilience study undertaken by Kaup and colleagues (2015). Focusing on PP, a continuous indicator of arterial stiffness, may have been more sensitive for our population. Maintaining good vascular health prevents the negative effects associated with hypertension, such as cerebral vascular damage and mini-infarcts, which can severely affect memory ability (Cooper et al., 2016). Notably, a recent study found that lower PP contributes positively to both cognitive reserve and memory performance (Alipour & Goldust, 2016). Furthermore, elevated PP is associated with increased AD-related cerebrospinal fluid biomarkers (i.e., Aβ and phosphorylated tau) (Nation et al., 2013). Maintaining vascular health likely plays a major role in promoting resilience to genetic risk by (a) preventing additional, vascular-related damage in the brain, (b) enhancing reserve, and (c) reducing Aβ- and tau-related neurodegeneration. Why this effect may be specific to females should be further investigated.

Higher PEF emerged as a genetically robust predictor of resilience in females and an important predictor in males with the highest form of genetic risk in our study (i.e., a high GRS). We can quantify relative level of risk within our population by looking at individual genetic risk scores based on allelic status. In our sample, the average GRS was 5.14 for males resilient to *APOE*, 3.39 for males resilient to *CLU*, and 5.49 for males resilient to a high GRS. Thus, PEF was an important predictor of resilience for males with the highest level of genetic risk. PEF assesses force of expiration and is an objective measure of aerobic fitness (Smith, Potter, McLaren, & Blumenthal, 2013). Like poor grip strength, decreased PEF is sometimes used as a marker of frailty (Sternberg, Schwartz, Karunananthan, Bergman, & Mark Clarfield, 2011). Because higher PEF predicted memory resilience in our sample, we further emphasize (a) the potential importance that preventing or avoiding frailty may play in promoting resilience to

genetic risk and (b) that physical fitness, at least objectively measured by functional biomarkers, is strongly associated with memory resilience in females. Notably, a recent study found that respiratory training improves cognitive function in the elderly (Ferreira et al., 2015). Although their results were for both females and males, other studies have also noted sex differences in PEF performance and change in older adults (Puts, Lips, & Deeg, 2005).

Finally, lower BMI predicted resilience in females with the *CLU* CC genotype and a high GRS. We found it interesting that BMI did not also predict resilience in females with the *APOE* ε4 allele because most (i.e., 83%) of the participants resilient to the *APOE* ε4 allele were also classified as resilient to a high GRS. Additionally, the respective average BMI was similar across all three resilience groups (see Tables 4.6, 4.8, and 4.10). We suggest two possibilities: (a) there is something specific about *CLU*-based resilience driving this effect or (b) resilience to *APOE* ε4 is more strongly predicted by other factors (for both *CLU*-and *GRS*-based resilience, BMI was relatively low in the prediction hierarchy). Nevertheless, lower BMI is related to our other indices of physiological health status. The lifestyle and physiological state associated with high BMI (i.e., obesity) likely contributes to poorer cognitive outcomes (Gunstad, Lhotsky, Wendell, Ferrucci, & Zonderman, 2010). Although not robust, our results suggest that older females with AD genetic risk may benefit from maintaining a healthy body weight along with healthy levels of other objective physiological indicators.

Broadly, our results within the functional biomarker domain suggest that females carrying AD genetic risk may benefit more than males from efforts to broadly improve or maintain their physiological health status. Possible interventions could target combined improvement in cardiovascular and general fitness, such as by encouraging physical exercise. Clinicians and researchers should note that frailty or poor physiological health in older females

may exacerbate the pathological effects of AD genetic risk on neurocognitive outcomes. For both males and females with genetic risk, preventing or reducing frailty (as assessed, at least in part, by GS and possibly by PEF) may be beneficial.

5.3. Health Characteristics

Only a few factors from our health domain emerged as important predictors of memory resilience. For females, better subjective health rating was a genetically robust predictor of resilience. Resilient females appear to be accurately aware of their relatively good health status (as indicated objectively by the biomarkers). We note, however, that maintained cognitive ability may conceivably play a role in the ability to accurately assess subjective health status.

Exclusively for males, a lower CES-D score (i.e., fewer depressive symptoms) was a genetically robust predictor of *APOE* and *CLU*-based memory resilience, but, oddly, it was not also a predictor of GRS-based resilience. Opposite to PEF results for males, the protective effect of a lower CES-D score seems to diminish for males with the highest genetic risk. Depression affects cognitive performance and may be a preventable risk factor for dementia (Wang & Blazer, 2015). Relevant to our study, the risk of MCI and dementia in cognitively normal adults that is associated with depression is (a) stronger in men, (b) enhanced in carriers of the *APOE* ε4 allele, and (c) related to plasma apolipoprotein J levels (Geda et al., 2006; Silajdzic, Minthon, Bjorkqvist, & Hansson, 2012). Furthermore, antidepressant use protects against memory and cognitive decline, particularly in males (Lipnicki et al., 2013). Interestingly, depressive symptoms are associated with cognitive decline independently of dementia-related neuropathology, implying that there are different underlying mechanisms (Wilson et al., 2014). Our results suggest that preventing or treating mood disorders such as depression may have

beneficial effects for aging males with AD genetic risk. However, this effect diminishes for males with high, combined AD genetic risk (i.e., a high GRS).

In our sample, diabetes status, head injury history, and statin use did not predict resilience for either sex in any case. However, we note that diabetes status and head injury were not tested as predictors in all groups due to low prevalence. For females, not taking anti-inflammatory medication predicted *CLU*-based resilience. It was low in the prediction hierarchy and not genetically robust so the benefit obtained from avoiding arthritis on memory resilience may be minimal, at least in our sample. We note that this factor was not tested as a predictor of resilience in any male genetic risk group because of low prevalence. Kaup and colleagues (2015) similarly found that cholesterol level, diabetes status, and level of inflammation were not important predictors of cognitive resilience for white older adults.

5.4. Mobility

Exclusively for females, both mobility factors (i.e., walking time and turning time) were important predictors of memory resilience and these effects were robust across genetic variants and the GRS. Neither mobility factor emerged as a predictor of resilience for males. Because physical fitness influences neuromuscular systems, physical health may be reflected by performance on mobility tasks that assess gait speed and balance (Laudani et al., 2013). Correspondingly, our mobility performance measures may also be related to our functional biomarker results which also showed sex-specificity in predicting resilience. Another study found that reduced walking speed was associated with cognitive impairment in older women (Sachdev et al., 2012). Carrying the *APOE* ε4 allele has even been associated with poorer performance on mobility tests in older adults (Melzer, Dik, van Kamp, Jonker, & Deeg, 2005). Our results further emphasize that older females with AD genetic risk may benefit from

maintenance or improvement in physical, physiological, and neuromuscular health from a variety of perspectives. There may also be a mechanistic relationship between resilience, fitness and mobility, and these apolipoproteins that could be further explored.

5.5. Lifestyle

From the lifestyle domain, greater participation in everyday novel cognitive activity was an important and genetically robust predictor of resilience across both sexes. It emerged as one of the most important predictors of resilience within most resilient groups. Maintaining a cognitively-stimulating lifestyle can promote resilience to age- and genetic risk-related EM decline by (a) enhancing cognitive reserve (Lachman et al., 2010) or plasticity (Runge, Small, McFall, & Dixon, 2014), (b) compensating for low educational attainment (Lachman et al., 2010), and (c) reducing AD pathology in genetic risk carriers (Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014). Because both everyday novel cognitive activity and level of education were important predictors of resilience in all six cases, we emphasize the role that cognitive reserve likely plays in promoting memory resilient phenotypes.

We also found that both social factors—more regular social visits (i.e., visiting family, friends, and neighbors) and volunteering more often—were genetically robust predictors of resilience in females. In contrast, socializing less (i.e., less social visits and volunteering less often) was predictive of *CLU*-based memory resilience selectively for males. It is possible that non-resilient males require more assistance from family and friends due to their declining cognitive status. Similar to the social-related demographic factors we tested, neither volunteering nor social visits predicted cognitive resilience to the *APOE* ε4 allele (Kaup et al., 2015) which could have been due to their mixed-sex analyses. Social factors have been previously associated with memory and cognition. For example, levels of social isolation and loneliness are both

negatively associated with memory performance, an effect which is enhanced in people with low education (Shankar, Hamer, McMunn, & Steptoe, 2013). Like lifestyle-related cognitive activities, social activities also contribute to cognitive reserve (Fratiglioni & Wang, 2007). In addition, some social activities can promote widespread lifestyle improvements (e.g., enhance physical activity). Recently, older females (but not males) that volunteered within a school system for two years spent significantly more time walking than those females that did not volunteer (Varma et al., 2016) . Such complex lifestyle activities (broadly classified as "social") may actually promote enhanced participation in social, cognitive, and physical activity which can, in effect, triply impact resilience and reserve. The mechanisms through which social activities promote cognitive reserve may vary across demographic groups, however, as this effect was specific to females in our sample.

Although markers of physiological health, fitness, and mobility emerged as genetically robust predictors of resilience in females, self-reported physical activity never emerged as a predictor of resilience for either sex. It is possible that our self-report questionnaire for participation in physical activity does not distinguish healthy older adults as well as objective biomarkers. Similarly, Kaup and colleagues (2015) did not find physical activity to be an important predictor of cognitive resilience. Their measure of physical activity was similar to ours in that it was self-report, but different in that they classified participants as having low, moderate, or high energy expenditure based on kilocalories per kilogram per week. It is possible that replacing the self-reported variables with objective measurements may yield different results (Celis-Morales et al., 2012). However, it is also possible that everyday physical activity is simply not a predictor of cognitive resilience (among races) or memory resilience (among sexes) in

older adults. Testing resilience within other cognitive domains (e.g., executive function) or with different methods of stratification (e.g., by age group) may produce different results.

Finally, current alcohol consumption predicted memory resilience in female *CLU* C homozygotes. Although there is some evidence that moderate alcohol consumption can protect against cognitive decline in aging (Baumgart et al., 2015), controversy exists for this relationship and genotypic effects (Kim et al., 2012). Our results do not implicate alcohol consumption as a strong or reliable predictor of memory resilience to AD genetic risk.

Taken together, the results we obtained within the lifestyle domain support the importance of maintaining an active lifestyle for memory resilience to genetic risk. Similarly, Ferrari and colleagues (2013) demonstrated that high participation in social, cognitive, and physical leisure activities prevents or delays dementia in *APOE* ε4 carriers, at least in part by increasing brain and cognitive reserve. In our sample, participation in cognitive and social activities promoted memory resilience to AD genetic risk, although differentially for females and males.

5.6. Interpretation and Implications

A major focus of this study was sex effects in predictors of resilience. Among both sexes, factors associated with cognitive reserve (i.e., level of education and everyday novel cognitive activity) were strong predictors of resilience to all forms of genetic risk. Given that cognitive activity and education were two of the top predictors of resilience in most cases, our results support that engaging in activities that boost cognitive reserve throughout the lifetime (e.g., higher education in young adulthood and cognitive activity in mid to older adulthood) is strongly implicated in providing resilience to risk factors in aging (Kemppainen et al., 2008; Reed et al., 2011), regardless of sex. Of note, we specifically investigated novel everyday cognitive

activities, which included activities such as playing bridge and doing taxes, as opposed to "passive" (e.g., reading the newspaper) or "integrative" (e.g., playing an instrument) cognitive activities. We reasoned that novel activities would have the greatest effect on resilience, given that they are more complex, stimulating, and cognitively-demanding. Our results indeed suggest that greater participation in complex everyday cognitive activities is beneficial, as has been found previously (de Frias & Dixon, 2014).

Examining sex differences in resilience to AD genetic risk in non-demented older adults may have implications for differential assessment and potential early interventions to reduce risk of cognitive decline and neurodegenerative disease. Specifically, understanding sex differences in risk and protective factors for resilience, decline, and neurodegenerative disease may aid in the development of individualized assessment, intervention, and treatment strategies (Mielke et al., 2014). As discussed, there are documented sex differences in cognitive performance throughout the lifespan, including older adult cognitive trajectories and AD risk (Li & Singh, 2014; McCarrey et al., 2016). Biological mechanisms for sex differences in AD prevalence—including varying pathological brain aging trajectories, onset of change, and mechanisms of risk—are beginning to be understood (Altmann et al., 2014; Zhao et al., 2016). Determining the biological basis in sex differences for cognitive aging and AD risk could potentially uncover new directions for reducing or preventing the risk of neurodegenerative disease, specifically in high-risk older adults.

We briefly report results from a recent study that support the multifactorial and sex-specific nature of our results. Artero and colleagues (2008) investigated sex-specific predictor profiles for MCI and conversion from MCI to dementia. In their sample, both females and males classified as MCI were more likely to have depressive symptoms (as measured with the CES-D

scale) and be taking anticholinergic medication. Females with MCI were more likely to (a) have poor subjective health, (b) have a disability, (c) be socially isolated, and (d) have insomnia. Males were more likely to have (a) a higher BMI, (b) diabetes, and (c) a history of stroke. They also tested sex effects in predictors of progression from MCI to dementia. For both females and males, declines in instrumental activities of daily living, carrying the *APOE* ε4 allele, low education, and older age predicted progression to dementia. For females, (a) subclinical depression and (b) taking anticholinergics also predicted progression. For males, history of stroke predicted progression (Artero et al., 2008). Other factors similar to those in our study (i.e., physical activity, current alcohol consumption, tobacco use, blood pressure [hypertension], history of head trauma) were not predictive of MCI or progression from MCI to dementia. Overall, they found that MCI can be differentiated by a large number of factors and that the factors differ for females and males. Notably, many of their sex differences in predictors of MCI or progression to dementia were similar to ours. They conclude that MCI is a common outcome of multiple aetiological pathways.

Our results also suggest possible complex sex differences in what promotes resilience. We briefly interpret and discuss the implications of the sex effects presented in this thesis. Similar to the Artero and colleagues (2008) study, our results suggest that although memory resilience is predicted in both sexes by some factors (e.g., high cognitive reserve, low frailty), memory resilience is a common outcome of multiple pathways that can differ substantially between males and females. In our sample, females had many more predictors of resilience than males. One possible reason for this could be the relative risk of the genes investigated, which may be stronger in females (Altmann et al., 2014; Farrer et al., 1997). However, testing other factors from these, or additional, domains could yield different results.

Notably, multiple indices of physical health (i.e., PP, PEF, and BMI) and both mobility factors (i.e., gait and balance) predicted resilience specifically in females, suggesting that there is a selective benefit of overall physiological and physical fitness for memory resilience in females with AD genetic risk. Moreover, resilient females appear to be aware of their relatively more favourable health status (because higher subjective health was an important predictor). There is evidence that various exercise training techniques (including aerobic, resistance, balance, and strength) benefit cognition through direct biological mechanisms (e.g., angiogenesis and neurogenesis) (Bherer et al., 2013; Hogan, Mata, & Carstensen, 2013; Nokia et al., 2016). Broadly, exercise and better overall health have beneficial effects on (a) brain structure and function, (b) sleep, (c) stress level, and (d) risk reduction for negative health outcomes (e.g., heart disease) (Bherer et al., 2013). Why this effect was specific to (a) females and (b) objective markers of physiological health and mobility (as opposed to self-reported physical activity) is unclear. It is possible that because older females are generally less active than males (Azevedo et al., 2007; DiPietro, 2001), they may benefit more from better physiological and physical health. As was shown in Table 4.5, we found that compared to females, males had significantly better PP, PEF, and GS as well as faster walking time.

Our results also highlight the importance of targeting multiple, modifiable risk factors for potential use as a panel of prevention of intervention targets (Figures 5.1-5.2). Like frailty indices (Song, Mitnitski, & Rockwood, 2011), we propose that methods to promote resilience to unmodifiable AD risk factors should consider approaches that take multiplicity of causes into account and, possibly, determine the underlying mechanisms. Anstey and colleagues (2014) recently developed the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI), a dynamic model that represents the network of influences on cognitive aging. The risk

index is a self-report tool to identify risk of AD and dementia. Briefly, it is an evidence-based composite risk score for AD and dementia derived from a number of validated risk and protective factors, many of which are similar to those used in this study. Specifically, it asks relevant demographic questions (e.g., age, gender, and education) and much more detailed questions about diabetes, history of head injury, lifestyle activities (cognitive, physical, social), smoking, eating habits, and depressive symptoms. Modifiable factors included in our study as well as the ANU-ADRI offer timely precision intervention targets for multi-factorial programs to sustain functional independence and delay cognitive impairment and decline, particularly in older adults with other, unmodifiable AD risk factors (Anstey et al., 2014). Non-invasive intervention strategies (including lifestyle and health improvement) for middle-aged and older adults are an easy and low-cost method of (a) promoting cognitive and memory resilience and (b) decreasing the risk of cognitive decline and dementia. Our study provides further evidence that risk management protocols, including risk reduction and protection elevation (e.g., resilience and reserve), should consider the multiple domains of risk and protection and the factors within that independently and interactively contribute to cognitive aging outcomes (Anstey et al., 2015). Given the evidence that AD risk (and potential for resilience) can be quantified, clinical practice guidelines may need to implement personalized risk-reduction assessments.

Very recently, an individualized, long-term, multifactorial approach lead to cognitive and functional improvements in *APOE* ε4 carriers diagnosed as having MCI or early AD (Bredesen et al., 2016). Dubbed Metabolic Enhancement for Neurodegeneration (MEND), the program had an array of targets that were individualized as needed (e.g., optimize sleep, reduce stress, improve diet, exercise, take vitamins, balance hormones) (Bredesen, 2014). Although the sample size was small ($n = 9$), there were marked improvements in neuropsychological performance,

functional ability, and, in one case, hippocampal volume (Bredesen et al., 2016) following the targeted intervention program. Altogether, the results of recent resilience research, the ANU-ADRI, and MEND suggest there may be merit in identifying genetically at-risk individuals in order to evaluate personalized delay, prevention, and intervention options from a wide array of easily modifiable factors (with the potential to promote resilience and healthy brain and cognitive aging). Even delaying age of onset (or slowing decline) of impairment and neurodegenerative disease will substantially reduce the societal and economic burden of cognitively-impaired and demented older adults (Anstey et al., 2015).

5.7. Limitations and Strengths

We note several limitations of the present study. First, we tested multiple predictor variables and, given that we stratified by sex and required participants to carry allelic risk, some cell sizes were relatively small. Although RFA is suitable for use in these circumstances (Strobl et al., 2009), we note that, like previous studies (e.g., Josefsson et al., 2012), null findings from promising domains (e.g., health) could be due to a lack of power. However, the present results are systematic and generally robust, suggesting stability of the phenomenon.

Second, VLS participants represent a relatively more advantaged segment of the population (e.g., high levels of education and standard of living, easy access to health care) (Dixon & de Frias, 2004). The intact nature of our sample may have decreased the strength of the factors associated with resilience. In other words, had our sample been more representative of a diverse population in terms of education and lifestyle some of the factors tested here may have emerged as important or relatively more important. Although the sample is not representative of all older adults, it provided a good estimation of adults in developed or western countries where the older segment of the population is rapidly growing. Our third limitation is related to the

second: We included a relatively homogenous group of older Caucasians which limits the generalization of these results across multiple races. Previous research has demonstrated differences in predictors of cognitive resilience within black and white older adults (Kaup et al., 2015) so future studies with more diverse populations could consider race-stratification.

Fourth, not all participants had an opportunity to provide a third wave of EM data; specifically participants in Samples 1 and 2 were only able to provide up to two waves of data. A more complete design would include nine years of data from all participants. Broader sampling could supplement prediction patterns. However, these data were only used for classification and missing data were imputed using gold-standard techniques. Fifth, we were only able to achieve partial scalar invariance of our EM latent variable (not full scalar or residual invariance, which would have been more desirable). However, our model fit statistics were adequate and we felt confident that our model was good enough to proceed.

Sixth, we investigated only two of many AD-related genes with the potential to influence EM in older adults. Based on a thorough review of extant literature, we chose these variants given their mechanistic similarities and known association with EM performance and change in aging adults. There may be merit in evaluating other relevant genotypes in future studies, including those with odds ratios more similar to *APOE* (e.g., *TREM2*). Seventh, some of our variables were limited by being self-report. Self-reported variables have the potential to bias results or not reflect objective measures. However, we expect that seriously misreported information was minimal and likely not systematically distributed in a manner that would bias our results. All of the present self-report measures have been used extensively and productively in the VLS and other projects. For example, other studies in AD risk assessment and risk reduction use combinations of self-report and objective variables and some relevant phenomena

can be efficiently assessed via self-report (Anstey, 2014; Anstey et al., 2014). Additionally, for the purposes of this study, we considered it better to have a large number of self-reported variables than a small number of objective measures. Nevertheless, in some cases, replication of findings using objective measures (e.g., physical activity) would clarify our results.

There are also several strengths of this study. First, we had a large, well characterized, and broadly assessed longitudinal dataset with an extensive 40-year band of aging (range: 53-95 years). Each participant contributed up to nine years of data. We collected comprehensive neuropsychological, demographic, biomarker, health, mobility, and lifestyle data from each participant, including those known to be associated with AD risk and protection. Second, we used multiple standard manifest variables to create a validated, longitudinal EM latent variable. Our longitudinal analysis of this latent memory score included two follow-up waves, which is desirable in longitudinal latent variable analyses.

Third, our approach limited EM practice effects (a major concern for longitudinal studies) by (a) having multiple word recall lists and rotating them through waves such that no participant saw the same list twice, (b) using more complex memory tasks (e.g., RAVLT and long memory lists), (c) combining multiple manifest memory measures into a latent variable, which reduces potential practice effects that could occur for any one indicator, (d) having long intervals between testing occasions (i.e., 4.5 years), and (e) achieving partial scalar invariance for our confirmatory factor analysis. Fourth, we employed contemporary statistical methods (including GMM and RFA) to most accurately and effectively investigate our research goals. More specifically, GMM allowed us to statistically uncover two latent groups of memory performance over time in order to define memory resilient participants. RFA allowed us to examine the relative importance of 22 AD risk factors from five validated AD risk domains in

predicting memory resilience. RFA is a novel multivariable analytic technique that revealed the factors most strongly predictive of resilience which may have potential as future intervention targets.

5.8. Future Directions

This thesis research was driven by the desire to investigate ways in which older adults with non-modifiable genetic risk can remain resilient to memory decline. Our results support the goal of reducing risk and promoting healthy brain aging in genetically at-risk older adults. Prevention strategies to increase or sustain healthy brain and cognitive aging should be started early, before the onset of MCI or AD. Future intervention studies could select individuals with AD genetic risk and conduct a broad risk assessment that includes modifiable factors (Anstey et al., 2015). Several of the factors identified by Anstey and colleagues (2014) are included in the present study. Our results suggest that intervention studies would benefit from the use of multi-factorial protocols that target modifiable factors with independent and interactive influences for all adults. Additionally, tailoring the prevention protocol to reflect sex differences in predictors and mechanics of cognitive and memory resilience would increase precision. A very large, long-term intervention study that considered the effect of sex, age group, and ethnicity would be beneficial. Complementing the work of Kaup and colleagues (2015), our random forest analyses provide groundwork for future studies to selectively evaluate the most important predictors (or domains of predictors) of resilience by sex, ethnicity, and genotype. For example, mobility and physiological health could be further explored for their predictive, mechanistic, and preventative potential in females with AD genetic risk. Further study of factors associated with resilience to non-modifiable genetic risk will elucidate or support modifiable options (e.g., vascular health,

novel cognitive activity) to promote cognitive maintenance or reduce the risk of cognitive decline.

Future studies could also investigate resilience to other AD risk genes (e.g., *TREM2*) and within other cognitive domains (e.g., executive function). A greater understanding of the specific mechanisms underlying resilient phenotypes may be beneficial for potential targeting treatments. Studies that follow-up on the sex effects presented here should attempt to recruit more male participants so that analyses can be done on samples more comparable in sample size and age range. Future studies may also benefit from investigating timing effects. For instance, should intervention studies be started in middle age or can they provide resilience to cognitive and memory decline even when initiated in late life? Further and more specific understanding of resilience phenotypes will enable us to promote healthy brain aging or delay cognitive decline and neurodegenerative disease, allowing older adults to maintain their functional independence for as long as possible.

In sum, our study highlights the importance of (a) using longitudinal trajectories to establish common phenotypes, (b) the value of studying brain and cognitive resilience as well as decline and impairment, (c) considering sex differences in brain, cognitive, and dementia aging research, and (d) assessing and targeting multiple, modifiable risk factors.

5.9. Conclusion

Our main objective was to determine if memory resilience to AD genetic risk is predicted by factors that are sex-specific and genetically robust. First, we differentiated a higher and stable nine-year memory trajectory group and established that resilient participants exist within this group despite the presence of specified AD risk alleles. Second, we found that several AD risk factors (i.e., age, education, grip strength, and novel cognitive activity) predict memory

resilience in both sexes but a greater number and wider breadth of factors applied only to females (Figure 5.1). Third, our predictor profiles were similar across the two AD risk genotypes (i.e., genetically robust) and the GRS for both sexes. Our results suggest that memory resilience in older adults carrying AD genetic risk may be optimally promoted by multi-factorial interventions that target modifiable factors from a variety of relevant domains. Intervention strategies for both female and male older adults should aim to increase cognitive reserve (e.g., higher education, more everyday novel cognitive activities) and prevent frailty (e.g., as assessed by grip strength) (Figure 5.2). Females carrying AD genetic risk may especially benefit from early clinical interventions that target broad improvements in physiological health (e.g., cardiovascular) and emphasize the importance of participating in diverse social activities. Males with AD genetic risk may also benefit from the treatment or prevention of depression or depressive symptoms.

We highlight the importance of (a) integrating sex-specific differences in normal, impaired, and resilient brain and cognitive aging research and (b) targeting multiple, modifiable factors for potential use as a panel of risk-reduction intervention targets to promote healthier brain aging. As recently expressed by the Alzheimer's Association, there is sufficient evidence that modifiable risk factors may be associated with reduced risk of dementia (e.g., physical and cardiovascular health, cognitive activity) such that a multivariate approach to risk reduction in which multiple lifestyle (e.g., physical activity) and health (e.g., cardiovascular) factors are targeted may be widely beneficial (Baumgart et al., 2015). By identifying predictive or modifiable factors that contribute to resilience, our results contribute strategies to promote high functional capacity and prevent or delay cognitive decline and dementia which is especially crucial for those individuals with non-modifiable genetic risk.

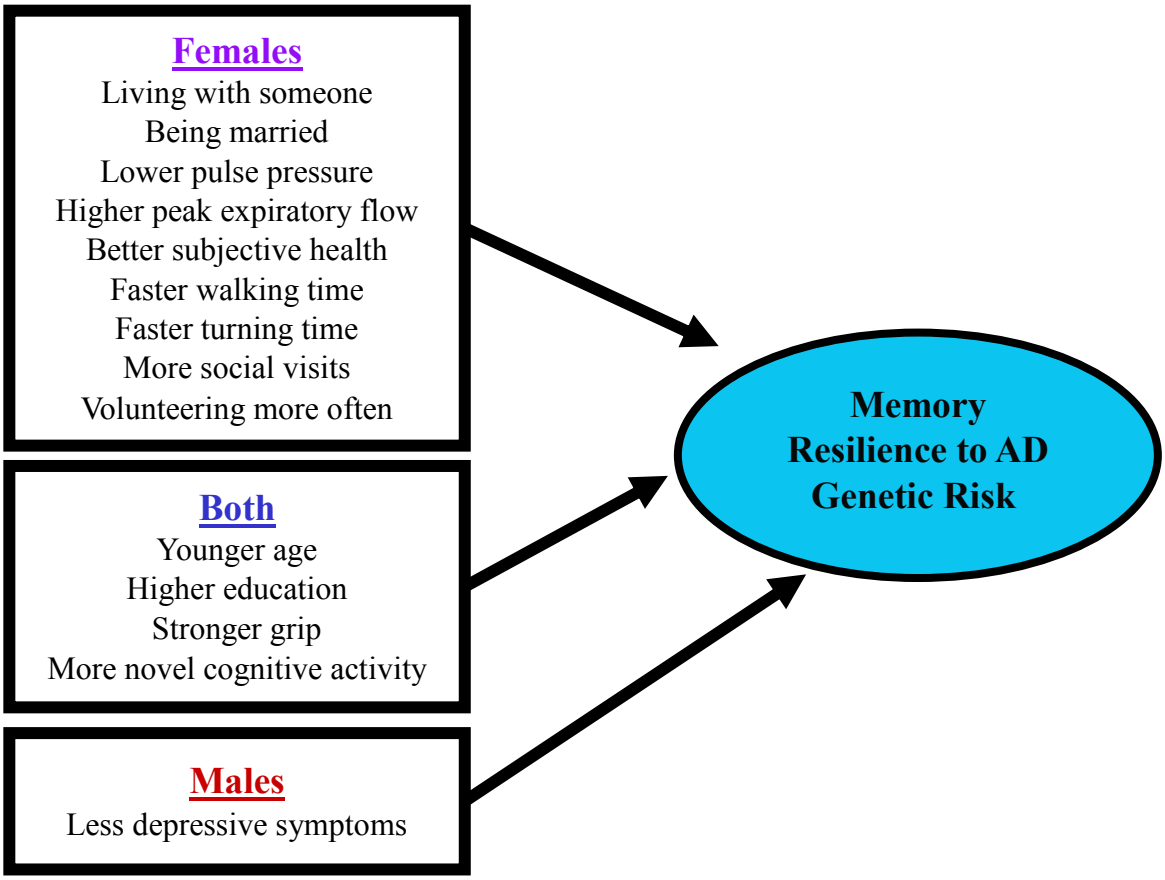


Figure 5.1. Genetically robust predictors of memory resilience to Alzheimer's disease (AD) genetic risk by sex. These factors were important predictors of both *APOE*- and *CLU*-based resilience. In most cases, they were also predictors of GRS-based resilience. However, we note that less depressive symptoms was only predictive of *APOE*- and *CLU*-based resilience (not GRS-based resilience) for males.

Figure 5.2. Possible intervention or prevention strategies to promote memory resilience in carriers of Alzheimer's disease (AD) genetic risk.

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