Cognitive Resilience to Frailty and Mobility Adversities in Aging:

Data-Driven Approach to Classification and Prediction by Risk Factors for Alzheimer's Disease

by

Sherilyn Thibeau

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Psychology

University of Alberta

Abstract

Objective: The overall aim of the current dissertation was to examine how and why some older adults maintain their cognitive performance for long periods of time, despite the presence of physical adversity factors known to be associated with the deterioration of cognitive function. We examined this general question in three longitudinal studies, organized into chapters. In Chapter Two, we examined the effect of frailty on three domains of cognitive performance and change (i.e., memory, speed, and executive function (EF)), as stratified by sex and *Apolipoprotein E* (*APOE*). In Chapter Three, we tested cognitive resilience to frailty across the three cognitive domains. Additionally, we investigated predictive factors that distinguish individuals with resilience to frailty from those without resilience. In Chapter Four, we investigated cognitive resilience to low mobility across the three cognitive domains. We also tested a set of predictive factors for distinguishing individuals with resilience to low mobility from those without resilience.

Overall Method: For the three chapters, we assembled a sample of non-demented, community-dwelling, older adults (n = 632, M age = 71, age range = 53 – 95) from the Victoria Longitudinal Study (VLS). From this source sample we drew slightly different study samples for each chapter. In Chapter Two, we used latent growth modeling to establish the effect of frailty on cognitive performance and change as well as moderation analyses to establish the effects of *APOE* and sex on frailty-cognition relationships. For Chapter Three, we used two data-driven technologies, latent class growth analyses (LCGA) and random forest analyses (RFA), to (a) establish classes of relatively high and low frailty, (b) establish subclasses of resilience and non-resilience to frailty, and (c) identify salient predictors discriminating between the resilient and non-resilient

classes. For Chapter Four, we used the same analytic technologies to test a similar set of research goals with respect to another physical health adversity, viz, low mobility.

Results: We summarize the results separately for each chapter. *Chapter Two*. First, frailty levels predicted speed and EF performance and differential memory change trajectories. Second, change in frailty predicted rate of speed and EF decline. Third, sex moderation analyses showed that females were selectively sensitive to the effects of (a) frailty on memory change, and (b) changing frailty on speed slopes. Additionally, the effect of frailty on EF trajectories was stronger for males than females. Fourth, *APOE* genetic risk carriers were selectively sensitive to the effects of frailty on the rate of memory decline. *Chapter Three*. First, we differentiated between individuals with frailty from those who were non-frail, based on the LCGA with an algorithm of level and slope. Second, using the frail class, we used the same analytics to establish subclasses of cognitively resilient and non-resilient individuals, separately for memory, speed, and EF domains. Third, we used RFA to determine the best predictors discriminating the resilient from non-resilient subclasses in each of the three cognitive domains. The following predictors discriminated memory resilience to frailty: high education, female sex, being married, high cognitive activity, and alcohol use. Three factors distinguished EF resilience to frailty: younger age, high education, and high cognitive activity. Additionally, one factor discriminated between resilient and non-resilient subclasses, high cognitive activity. *Chapter Four*. First, we differentiated between individuals with low mobility from those with high mobility, based on the LCGA with an algorithm of level and slope. Second, using the class with low mobility, we established subclasses of cognitively resilient and non-resilient individuals in each of the cognitive domains. Third, the following factors differentiated between cognitively resilient and non-resilient older adults. For memory resilience to low mobility, high education, alcohol use,

high cognitive activity, high physical activity, no depressive symptoms, high peak flow, and *APOE* non-risk status discriminated resilient from non-resilient subclasses. For speed resilience to low mobility, younger age, high education, high social activity, high peak flow, and high subjective health discriminated between resilient and non-resilient subclasses. For EF resilience to low mobility, younger age, high cognitive activity, high social activity, high volunteer activity, and low pulse pressure (PP) discriminated between resilient and non-resilient subclasses.

Discussion: Frailty and mobility present typical adversities to aging adults. In Chapter Two, we showed that higher frailty was associated with worse cognitive performance and change, and this relationship differed according to sex and *APOE* genetic risk status. In Chapter Three, we empirically characterized cognitive resilience to frailty, and established factors that predicted resilience. In Chapter Four, we empirically characterized cognitive resilience to low mobility and established factors predictive of resilience to low mobility. For older adults, developing cognitive resilience despite the presence of physical health adversity offers great potential for AD risk reduction targets. Regarding frailty resilience, such potential modifiable targets include high cognitive activity and high education. Regarding mobility resilience, such potential modifiable targets include high education, high cognitive activity, high social activity, high peak flow, and younger age. Pinpointing and increasing conditions that are protective to cognitive functioning (and contribute to sustained cognitive resilience) has enormous potential to delay the onset of cognitive decline and dementia, despite the common aging adversities of frailty and mobility decrements.

Preface

Chapter Two and Appendix A of this dissertation proposal have been published as S. Thibeau, K. McDermott, G. P. McFall, K. Rockwood, and R. A. Dixon, "Frailty Effects on Non-Demented Cognitive Trajectories are Moderated by Sex and Alzheimer's Genetic Risk," *Alzheimer's Research and Therapy*, 2019, issue 1, 1-55. doi: https://doi.org/10.1186/s13195-019-0509-9. ST, KM, RAD, and KR were responsible for the conception and background. ST, KM, GPM, and RAD were responsible for the design and analysis plan. ST and GPM were responsible for the data assembly and statistical analyses. ST, GPM, and RAD were responsible for the result interpretation. ST drafted the manuscript. GPM, RAD, and KR critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript. This is the final accepted version of the pre-publication manuscript and supplementary material.

Dedication

To my beloveds,

our resilience is the result of constant course correction amid the storm.

I deeply adore each of you and attribute this to your unfailing encouragement and support.

Acknowledgements

This dissertation is the result of a long, arduous process that involved contributions from many people. I am deeply grateful to those who have helped me along this journey. First and foremost, to my supervisor, Dr. Roger Dixon. I would like to thank Dr. Dixon for providing mentorship, feedback, guidance, challenge, and flexibility as I have travelled this lengthy, non-linear journey. To Drs. Camicioli and Wiebe, my supervisory committee members, who have provided direction, insight, and differing vantage points from which to improve my research. I offer special thanks to my lab allies: Jill, Peggy, Sebastian, Shannon, and Linzy. Thank you all for sharing wisdom, expertise, coffee, laughter, and inspiration. Finally, to my friends, my family, my tribe. I would not be who I am without you.

Funding Acknowledgment. The research reported in this dissertation by Sheri Thibeau has been supported by grants to Roger A Dixon from: (a) Canadian Consortium on Neurodegeneration in Aging in partnership with Alberta Innovates and the Canadian Institutes of Health Research, (b) National Institutes of Health (National Institute on Aging; R01 AG088235), and (c) the Canada Research Chairs program.

Table of Contents

List of Tables

List of Figures

Abbreviations

-2LL – -2 Log Likelihood

AD – Alzheimer's Disease

AIC – Akaike Information Criterion

APOE – Apolipoprotein E

BDNF – Brain-Derived Neurotrophic Factor

BIC – Bayesian Information Criterion

BMI – Body Mass Index

CFA – Confirmatory Factor Analysis

CFI – Comparative Fit Index

CHELM – Cognitive Health and Lifecourse Model

CLU – Clusterin

D – Deviance Statistic

df – Degrees of Freedom

DMA – Declining Memory Aging

EF – Executive Function

EM – Episodic Memory

FI – Frailty Index

LCGA – Latent Class Growth Analysis

MCI – Mild Cognitive Impairment

MMSE – Mini-Mental Status Exam

NMA – Normal Memory Aging

PP – Pulse Pressure

REY – Rey Auditory Verbal Learning

RFA – Random Forest Analysis

RG – Research Goal

RMSEA – Root Mean Square Error of Approximation

SMA – Stable Memory Aging

SRMR – Standardized Root Mean Residual

VLS – Victoria Longitudinal Study

W – Wave

$\Delta\chi 2$ – Change in Square

Δdf – Change in Degrees of Freedom

$\chi 2$ – Chi-Square Test of Model Fit

Chapter One: Conceptual Framework

The purpose of this conceptual framework is to identify and integrate the key theoretical underpinnings, methodological approaches, and empirical bases of the programmatic set of studies assembled for this dissertation. This framework links diverse, yet interconnected, areas within the overarching discipline of cognitive aging, providing the foundation which guides and informs this dissertation research. Accordingly, section one summarizes the urgent problem of brain aging and dementia from a population perspective and links it to the approach followed in the present research. The second section presents a comprehensive review of the key literature, major findings, and methodological considerations of empirical evidence pertinent to the emerging area of cognitive resilience. The third section integrates the topics covered in the review in order to summarize the three longitudinal studies, providing a roadmap of the research goals and implications of each study. The fourth section presents the significance of this comprehensive research.

Section One: Rationale and Goals of the Project

Population aging is one of the most momentous transformations of the 21st century, with vast economic, health, and social ramifications (United Nations, 2015). Human longevity has increased globally over the past 50 years, with life expectancy reaching a world-wide average of 70 years (Jin, Simpkins, Ji, Leis, & Stambler, 2015). As the 'greying of the population' increases, disease and mortality patterns are shifting worldwide as well (Beard et al., 2016). There are currently 50 million people living with dementia worldwide, and within the next 30 years this number is projected to reach 152 million (World Health Organization, 2018). Alzheimer's disease (AD) is the most common form of dementia and is now the fifth leading cause of death worldwide. This is a striking shift, as AD did not rank within the top ten causes of

death only a decade ago (World Health Organization, 2018). Economically, the total global societal cost of caring for individuals with dementia was $818 billion (USD) in 2015, and the cost is projected to double within the next decade (World Health Organization, 2018). This economic burden will continue to increase rapidly unless there are significant reductions in the number of dementia cases (Alzheimer Society of Canada, 2015). Notably, even delaying the onset of dementia by five years would drastically reduce the prevalence of dementia and alleviate this substantial economic burden (Fratiglioni & Wang, 2007). Unfortunately, there are no disease-modifying treatments; psychopharmacological approaches have proven unsuccessful despite the time, money, and effort invested (Cummings, Lee, Ritter, & Zhong, 2018).

Population aging, the subsequent increase in dementia, and the lack of a pharmaceutical solution has prompted focus on AD prevention and early diagnosis. Fortunately, AD has a long prodromal phase which presents an extended period of brain aging where cognitive trajectories may be malleable to intervention (Isaacson et al., 2018; McFall, McDermott, & Dixon, 2019; Sheng, Huang, & Han, 2018; Wilson, Leurgans, Boyle, & Bennett, 2011). Accordingly, prevention methods aimed at maintaining brain and cognitive health and delaying dementia in a non-demented population have come to the forefront of aging research (Anstey, Ee, Eramudugolla, Jagger, & Peters, 2019; Brayne & Richard, 2019; Deckers et al., 2019; Heffernan et al., 2019; Sexton & Yaffe, 2019). To advance prevention approaches, many studies have focused on identifying factors within normal aging which either confer protection against or increase risk for AD across several domains (e.g., lifestyle, genetic, biological, health). To date, secondary prevention methods (such as interventions) may focus on risk-reduction, enhancing protection, or a combination of both strategies to slow or halt the progress of cognitive decline for those at risk of developing dementia. For example, a recent randomized control trial (RCT)

examined the cognitive effect of a multi-domain intervention for older adults at risk of developing dementia, prior to the onset of any neurodegenerative diagnosis. The intervention focused on enhancing protection by improving diet and increasing participation in cognitive, social, and physical activity, while also reducing AD risk factors (i.e., poor vascular health; Ngandu et al., 2015). Their novel results indicated that those who participated in the intervention had greater improvement in scores on a neuropsychological test battery than those in the control group. These results indicate that focusing on increasing protective factors and reducing dementia-related risk factors is a reasonable target for supporting cognitive and brain health.

Although intervention approaches aimed at enhancing protection may be effective, risk-reduction may not always be a feasible target as not all risk factors can be altered or modified. For example, biological (i.e., sex) and genetic (i.e., *Apolipoprotein* ε4; *APOE* ε4) risk factors are not modifiable, and therefore play a different role within a risk-reduction approach. Specifically, as powerful but non-modifiable risk factors for cognitive decline and impairment, they are often included as predictors and moderators in research designs. Additionally, some risk factors may be indicators of complex pathophysiological processes of decline already established in the individual (e.g., increasing frailty or declining mobility levels), which are not easily amenable. To add further complexity, non-modifiable risk factors also influence the extent to which protective factors act on cognitive performance and decline. For example, *APOE* genetic risk status has been found to influence the effect that physical activity has on cognitive function (Jensen et al., 2019; Thibeau, McFall, Wiebe, Camicioli, & Dixon, 2017).

Considering these complexities, a shift toward a salutogenic model for brain and cognitive health may be warranted. A salutogenic orientation, when applied to cognitive aging, assumes that each individual is characterized by risk factors for cognitive decline, but focuses

instead on the ‘general resistance resources’ that explain the movement towards or maintenance of cognitive health (Antonovsky, 1996). A salutogenic model of cognitive aging encompasses multidimensional approaches to creating conditions for promoting and optimizing cognitive health, prior to the onset of AD. Current examples of approaches embodying the salutogenic orientation to cognitive aging include the examination of reserve, healthy or successful brain aging, and the emerging concept of resilience. This dissertation will focus on the latter of the three.

Resilience in aging has been defined as the ability to maintain or regain sustained levels of functioning despite adversity (Baltes, 1987; Dixon & Lachman, 2019; Wagnild & Collins, 2009). While there is a lack of a common definition when applied to cognitive aging, resilience may be conceptualized as the ability to maintain cognitive function over time, despite the presence of risk factors that are detrimental to brain function and health (Anstey & Dixon, in press). A resilience framework focuses on increasing other facets of health that confer resilience even when risk factors for cognitive decline are present. Accordingly, developing resilience may be very accessible to older adults, regardless of the presence of risk factors or physical health adversities which confer high risk for cognitive decline (Anstey & Dixon, in press). Notably, two recent studies have examined factors that are predictive of cognitive resilience to genetic risk for AD. The results from both studies indicated several factors from lifestyle, psychosocial, health, and demographic domains foster cognitive resilience to AD genetic risk (Kaup et al., 2015; McDermott, McFall, Andrews, Anstey, & Dixon, 2017). Similar factors conferring resilience in both studies included higher education and higher cognitive activity. Upon consideration, it is important to examine whether factors that increase cognitive resilience are dependent on the adversity being examined. For example, while education and cognitive activity are predictors of

resilience to AD genetic risk, it is unknown whether these factors are predictors of resilience to adversities with more complex physiological underpinnings, such as frailty and mobility impairment. Conceptually, it is possible that the adaptations required to achieve cognitive resilience in the face of physical health adversities may be distinct from the factors that confer resilience to genetic risk.

This dissertation uses the salutogenic approach to examine cognitive resilience despite the presence of significant physical health deficits in a non-demented population. The general aim of this dissertation is to examine how and why some older adults maintain their cognitive health and performance for long periods of time, even though they have significant physical health adversities known to be associated with the deterioration of cognitive function. This aim is systematically operationalized through three longitudinal studies which are organized into chapters that provide the context and framework for examining cognitive resilience to frailty and (separately) mobility impairment. Chapter Two will establish frailty as a risk factor to cognitive performance and longitudinal trajectories across three cognitive domains: namely, memory, speed, and executive function (EF). An important feature is that the relationship between frailty and cognition is examined through stratification of individuals by previously established AD risk factors (i.e., *APOE ε4* genetic status and female sex). This moderation analysis allows the cognitive trajectories to be compared between risk and non-risk groups, depicting differing cognitive trajectories according to multiple levels of AD risk. Chapter Three builds upon Chapter Two by examining cognitive resilience to frailty across the same three cognitive domains. In this chapter we will identify individuals who have higher levels of frailty and classify them into those who are resilient (or not) in that they maintain cognitive function over time despite this adversity. Subsequently, we also examine whether there are predictive factors unique to the resilient group.

A central feature of this chapter is the identification of a set of factors that confer protection against the negative effect that frailty has on cognitive performance. Chapter Four applies the same theoretical and statistical framework to a separate and distinct physical health adversity known to have a detrimental effect on cognition (i.e., low mobility). In this chapter, we will identify older adults with low mobility levels who are nevertheless resilient in that they are able to maintain their performance in (separately) three domains of cognition despite the adversity. As in Chapter Three, the next step will be to identify factors that are predictive of cognitive resilience to low mobility.

The latter two chapters include parallel components of resilience prediction. As in previous research (Kaup et al. 2015; McDermott et al., 2017), machine learning technology is used for the prediction analyses. McDermott and colleagues (2017) included a panel of 22 predictors from five domains (i.e., demographic, functional, health, mobility, and lifestyle domains). Kaup and colleagues (2015) included a similar set of predictors from demographic, health, and lifestyle domains. Following these approaches, a set of predictors were selected and used to compare common factors that determine resilience in each of the domains of cognition, across both common physical health adversities. Specifically, we included all but two of the predictors (i.e., head injury and statin use) that McDermott and colleagues (2017) used in their research (see Table 1-1). Additionally, we added two genetic factors associated with cognitive aging and resilience, namely *APOE* and Brain-Derived Neurotrophic Factor (*BDNF)*. We also note that several of the predictors that Kaup and colleagues (2015) used in their research were not available in the Victoria Longtudinal Study (VLS; e.g., sleep time, financial status, literacy level) so we were not able to consider them for inclusion in our research. Therefore, in total we considered 22 initial predictors from four risk domains: demographic, lifestyle, genetic, and

functional health (see Table 1-1 for a comparison of the predictors used in this dissertation, Kaup et al., 2015, and McDermott et al., 2017). Specifically, demographic factors were each participant's (a) age in years, (b) marital status, (c) education (total years) (d) sex (male or female), (e) living status, and (f) pet ownership. Lifestyle factors are (a) everyday novel cognitive activity, (b) social activity, (c) volunteer activity, (d) physical activity, (e) alcohol use, and (f) smoking. Genetic factors are risk or non-risk status for the following genes (a) *APOE* and (b) *BDNF*. Functional health factors are (a) pulse pressure (PP), (b) body mass index (BMI), (c) diabetes, (d) peak flow, (e) grip strength, (f) anti-inflammatory medication, (g) depression, and (h) subjective health. Once these predictors were established, an important consideration was the identification of predictors which are also components of the frailty index. Upon review of this consideration, we were not able to use 9 of the 22 factors in Chapter Three, which examines cognitive resilience to frailty. Specifically, the factors that were also components of the frailty index (and therefore could not be considered as predictors of frailty resilience) were eight factors within the functional health domain and physical activity from the lifestyle domain. The 13 'core' predictors used in Chapters Three and Four and the 'additional' physical health factors included on Chapter Four are listed in Table 1-2. Notably, the inclusion of all 22 original factors in Chapter Four offers the opportunity to test predictors of resilience to declining mobility which may not be available to individuals with an overall accumulation of health deficits. For example, cognitive resilience may be fostered by maintaining grip strength or higher peak flow for an individual with low mobility, whereas it is likely a highly frail individual would have already experienced a decline in grip strength and respiratory function. As such, while there may be common predictors of resilience for both groups, a highly frail individual may experience added

barriers to engaging in modification of health factors, providing a necessity for precision targets to increase resilience in this subpopulation.

Overall, when taken together, the three chapters included in this dissertation will (a) establish the risk of frailty to cognitive performance, (b) determine whether individuals can maintain cognitive performance despite declines in physical health (i.e., frailty and mobility), and (c) identify both common and distinct factors which foster cognitive resilience in older adults with either frailty or low mobility. Notably, cognitive resilience to AD risk may be an indicator of healthy brain aging (Dixon & Lachman, 2019). Systematically detecting and identifying individuals who are cognitively resilient and examining these unique trajectories over time allows researchers a promising opportunity to define, describe, and explain this emerging and potentially powerful construct. In addition, identifying a core set of factors that predict resilience allows several opportunities for key comparisons to be made and tested across adversities associated with cognitive decline, impairment, and AD. For example, subsequent research could examine whether the same core set of predictors fosters cognitive resilience to other adversities, such as diabetes or high blood pressure. Accordingly, identifying common predictors of cognitive resilience to AD risk has the potential for generalized recommendations to be made for promoting brain and cognitive health for older adults. Moreover, detecting unique factors that are predictive of resilience to specific types of AD risk fosters an opportunity for precision intervention for older adults (Dixon & Lachman, 2019). In sum, cognitive resilience offers a lens of substantial potential from which to examine healthy brain and cognitive aging, as it may occur in the context of common aging-related adversities.

Section Two: Key Literatures Informing Dissertation

Cognitive Aging Theories and Approaches

The field of cognitive aging refers to an area of research concerned with developmental changes across domains of cognitive function throughout the lifespan, especially adulthood and aging. As this field includes a wide collection of research on human cognitive behaviour from individuals over the age of 25, it is imperative to explicitly define overarching themes and theoretical approaches that inform this dissertation (Salthouse, 1991). Three longstanding, overarching themes within the science of cognitive aging are of particular importance and underlie the selection of the theoretical framework adopted in this dissertation (Dixon, 2011). Specifically, the core concepts used to steer the selection of theoretical approaches are (a) complexity (i.e., the disposition to examine complex processes), (b) aging change (i.e., the importance of viewing cognitive change as development across the life course), and (c) differential change (i.e., multidirectional changes in aging are characterized by individual differences and variability) (Dixon, 2011).

The longstanding theme of complexity in cognitive aging dictates that the theoretical framework for research must take into account the occurrence of multiple facets, levels, influences, directions, processes, predictors, precursors, trajectories, outcomes, contexts, and patterns of developmental changes that occur in aging (Baltes, Lindenberger, & Staudinger, 2006; Dixon, 2011; Hofer & Piccinin, 2010). Additionally, any aging change in cognition is a result of processes that unfold over decades, and requires longitudinal tracking, data, and methodology (Baltes et al., 2006; Baltes, Staudinger, & Lindenberger, 1999; Dixon, 2011; Hofer & Piccinin, 2010). Furthermore, a core task of the field is to characterize the differences seen between individuals, as well as the substantial variability within individuals over the course of adulthood. Although there are normative changes that take place across the lifespan, one must recognize and account for the vast diversity and difference with respect to age-related changes in

cognitive performance, change, rate of change, and final cognitive status (Dixon, 2011; Hertzog, 2008). Taken together, cognitive aging herein is operationally defined as a multidimensional, multidirectional process with considerable diversity and heterogeneity in the timing, trajectories, and etiologies over the lifecourse (Baltes et al., 2006; Dixon, 2000). Additionally, the attention of this empirical examination will be non-demented cognitive aging, primarily in the latter part of the lifespan.

The aforementioned themes provide the foundation for the selection of theoretical approaches informing this dissertation: (a) the individual differences perspective, (b) resilient brain aging, and (c) the cognitive health and environment life course model (CHELM; Anstey, 2014; Greenwood & Parasuraman, 2010; Hertzog, 2008; Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010; Negash, Wilson, et al., 2013; Willis, Schaie, & Martin, 2009). Collectively, these theoretical approaches and the CHELM provide the organization and direction that guide the research questions, statistical methodology, and interpretation of the research results.

Individual Differences Perspective. Viewing cognitive aging from the perspective of individual differences indicates that cognition changes in complex ways across and within individuals (Hertzog, 2008). According to this perspective, the critical information concerning cognitive changes with aging remains within the vast variability between and within individual performance. This perspective is informed by the initial focus on age differences in mean cognitive performance, building a more refined perspective of a very complex phenomena by isolating individual differences in cognitive change (Hertzog, 1985). Over the past few decades, research has shown that several adults have higher cognitive capacity and maintain their cognition for a long period, whilst others experience lower cognitive ability with varying rates of

decline across the last part of their lifespan. Applied to this dissertation research, this discovery has two main methodological implications. First, the issue of research design must be addressed. Cross-sectional research, while informative, does not allow for the observation of individual changes over time. This information is only offered through repeated measurements of the same individual across many years (i.e., longitudinal assessment). Second, an individual differences perspective requires use of methodology capable of identifying change and variation in change in cognitive performance as well as stability. Additionally, age-related changes in cognition vary between different cognitive functions (i.e., memory, EF, and speed) even for the same individual (Blazer, Yaffe, & Karlawish, 2015; Blazer, Yaffe, & Liverman, 2015). An individual differences perspective highlights the necessity to examine the multidimensionality of cognitive performance, due to the individual variability in performance and change within cognitive domains. Therefore, individual differences in cognitive aging are best studied with change-oriented research designs, using statistical methodologies which can quantify changes in a mean group level as well as individual differences across multiple cognitive domains. As such, the research in this dissertation utilizes a longitudinal design and modern statistical analysis procedures, such as structural equation modeling, growth mixture modeling, and Random Forest Analysis (RFA).

Resilient Brain Aging. An important concept in neuroscience and cognitive aging scholarship has been that neural resources may be used or developed to overcome age-related decline (Park & Bischof, 2013). The brain may be the most resilient organ in the human body, due to its capacity for neuroplasticity through synaptogenesis, neurogenesis, and angiogenesis. Resilient brain aging may have roots in positive psychology, and when paired with the concept of intra-individual neuroplasticity, highlights a capacity for human thriving despite adversity or

disease (Baltes, 1997; Seligman & Csikszentmihalyi, 2000). In the context of cognitive aging, resilient brain aging may be exemplified by an individual who maintains their cognitive performance over time despite detrimental influences on brain health, structure, or function. Examining brain resilience calls attention to an intricate network of interacting environmental, social, biological, psychological factors across lifespan development (Lavretsky, 2014). We know these factors may operate to influence brain and cognitive health in a variety of ways: independently, interactively, synergistically, antagonistically, or differentially (Montaine et al., 2019).

It is now well known that brain structure and function are strongly associated with cognitive function (Borelli et al., 2018; Duda & Sweet, 2020; Fan et al., 2019). For example, neuropathological biomarkers, such as amyloid deposition and cortical atrophy, have been strongly associated with cognitive decline and AD (Fan et al., 2018; Hohman et al., 2017; Jansen et al., 2018). However, little is known why some individuals with high neuropathological burden remain cognitively unimpaired (Corrada, Berlau, & Kawas, 2012; Negash et al., 2013; Wallace, Theou, Rockwood, & Andrew, 2018). Subsequently, an emerging goal of human aging research has been to understand the concept of brain resilience as a defence that may lead to optimal cognitive function despite adversity, such as high AD-related neuropathology (Negash et al., 2013). For example, Negash and colleagues (2013) quantified AD resilience as the discordance between neuropathology and global cognitive function. Their results also identified several factors that were associated with resilience, including higher education, higher reading level, and cognitive activity in early life. Moreover, they found that age, and *APOE* risk status was associated with lower AD resilience. More recently, Aiello Bowles and colleagues (2019) examined cognitive resilience to AD neuropathology in 591 deceased individuals who had

complete autopsy data. They operationally defined cognitive resilience as having intermediate or high neuropathological burden yet no clinical dementia diagnosis and a score of over 86 on a Cognitive Abilities Screening Instrument within two years of death. Additionally, they compared factors predictive of resilience between those defined as resilient and non-resilient. Their results indicated that higher education, higher brain weight at autopsy, hippocampal sclerosis, absence of Braak stage five or six and microinfarcts were all associated with resilience. Taken together, these results indicate that various factors may influence the maintenance of cognitive function in late-life and contribute to cognitive resilience to AD neuropathology.

Notably, the concept of resilient brain aging brings adversity directly into the equation through the underlying assumption that everyone has an accumulated profile of risk factors detrimental to brain health (Anstey et al., 2019; Lavretsky, 2014; Livingston et al., 2017). Hence, the theory of resilient brain aging uses a salutogenic orientation to focus scholarly inquiry on the facets that foster brain and cognitive neuroplasticity, despite the array of risk-profiles that may be present. It is important to note that the specificity of the risk profile may be unique to each individual. Therefore, the emerging literature must examine brain resilience to the range of factors known to pose a threat to brain and cognitive health. This dissertation utilizes a resilient brain aging approach to operationally define and examine cognitive resilience as maintenance of cognitive performance despite the presence of two specific physical health adversities, frailty and low mobility. The newly generated information will contribute to the emerging body of research necessary to understand the complex relationships between brain resilience and AD risk.

Cognitive Health and Environment Life Course Model (CHELM). The CHELM has produced a framework for understanding the complexities which yield the wide variability of cognitive trajectories (Anstey, 2014). This model arises in response to research that has

identified several influences from a variety of domains that affect brain and cognitive health. While much of the research links these influencing factors to dementia independently (Dekhtyar, Wang, Fratiglioni, & Herlitz, 2016; Nagai, Hoshide, & Kario, 2010; Ott et al., 1998; Singh-Manoux et al., 2018), we now know that these factors co-occur and interact with one another (Morris, D'Este, Sargent-Cox, & Anstey, 2016; Shaaban, Jia, Chang, & Ganguli, 2019; Wagner et al., 2018). The CHELM provides the theoretical framework which incorporates the empirically identified factors along with possible avenues of interaction and influence, producing the range of cognitive trajectories seen in older adulthood. Key aspects of the CHELM relevant to this dissertation are noted here. First, the CHELM identifies that particular factors confer protection (are risk-reducing) yet act in combination with risk-enhancing factors (Anstey, 2014; Livingston et al., 2017). Second, the CHELM model identifies that influencing factors may be amenable to change or modification (such as cognitive activity level) or may be static, unchangeable influences (such as sex or genetics). Third, the CHELM suggests that adoption of the lifespan perspective is essential in cognitive aging research, as longitudinal follow-up is necessary to describe and differentiate the various cognitive phenotypes in later adulthood (Anstey, 2014), prior to the onset of neurodegenerative diseases. Therefore, the proposed studies in this dissertation examine a combination of modifiable and non-modifiable factors as they influence various cognitive domains over several years, prior to the onset of neurodegenerative conditions.

Three Cognitive Domains Relevant to Aging

The three main major cognitive domains affected by aging are episodic memory, speed, and EF (Buckner, 2004; Dixon et al., 2007). Notably, there is no fixed pattern for age-related cognitive change, as normative age-related changes occur differentially across cognitive domains

(Small, Dixon, & McArdle, 2011). This next section discusses three age-sensitive cognitive domains: memory, speed, and EF.

Memory. A fundamental change in cognition that occurs with advancing age is a decline in the ability to encode, store, and retrieve personally relevant events situated in time and place (i.e., episodic memory; Klaming, Annese, Veltman, & Comijs, 2017; Tromp, Dufour, Lithfous, Pebayle, & Després, 2015). Memory is primarily dependent on a vast network of brain regions that are very sensitive to age-related changes (i.e., the medial temporal lobe (particularly the hippocampus), prefrontal cortex, and posterior cortical regions; Rugg & Vilberg, 2013; Tromp et al., 2015; Wang & Cabeza, 2016). As such, episodic memory is thought to be the one of the most age-sensitive systems, with older adults experiencing declines (on average) around age 60-70 years of age (Dixon, Small, MacDonald, & McArdle, 2012; Nyberg, 2017). However, just as age-related structural brain changes are not uniform across individuals, there is substantial variability in memory trajectories among older adults (Dixon et al., 2012; Glisky, 2007). Some older adults may experience stable memory performance with very little decline, some may experience typical age-related decline, while still others may experience accelerated memory decline associated with preclinical and clinical AD (Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012; L. Nyberg, 2017; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). For example, a 15-year longitudinal study by Josefsson and colleagues (2012) showed substantial variability within memory trajectories of healthy (non-demented at baseline) older adults from the Betula project. Their results indicated that almost 20% of participants maintained high memory performance, over two-thirds experienced typical memory decline, and 13% declined faster than their age-matched peers. Moreover, a longitudinal examination of memory trajectories by McFall and colleagues (2019; see also Dixon et al., 2012) indicated that the

patterns of change for non-demented older adults are markedly diverse, reflecting highly variable individual trajectories across time, even when stratified by age into Young-Old and Old-Old adults. In this recent research, memory trajectory analyses differentiated three subclasses of memory trajectories based on performance and change. These three subclasses were Stable Memory Aging (SMA) which was characterized by above average level and sustained memory slope, Normal Memory Aging (NMA) which was characterized by an average level of performance and a moderately declining slope, and Declining Memory Aging (DMA) which was characterized by a lower-than-average performance and a substantial decline in memory over time. In their research, the variability in memory trajectories for non-demented older adults was explained by various combinations of risk and protective factors. For example, they differentiated the relative importance of seventeen predictors in discriminating the three memory classes. The 17 predictors considered in their research were from four domains (i.e., demographic, functional health, lifestyle and psychological) and included age, education, living status, sex, PP, peak expiratory flow, grip strength, BMI, heart rate, subjective health, depressive symptoms, timed walk, timed turn, cognitive activity, social activity, physical activity, and self maintenance activity. Indeed, the predictors of stable memory aging were different than those predicting declining memory aging. For example, female sex, higher education, higher cognitive and social activity were all predictors of SMA in both age strata, while the only common predictor of DMA in both age groups was lower participation in novel cognitive activities. In comparison with the present research, 13 of the 17 predictors McFall and colleagues included in their study overlap with predictors included in this dissertation (see Table 1-3). Additionally, three of the remaining predictors used by McFall and colleagues were used in the present research as components in the frailty index (namely timed walk, timed turn, and resting heart

rate; see Table 2-3 for the frailty index). General self-maintenance activity (which includes doing housework, preparing meals, taking care of a pet, shopping for food, shopping at a mall or downtown, and taking care of a family member) was not included in this dissertation as a predictor of cognitive resilience. However, we included pet ownership as a predictor of cognitive resilience and included measures of ability to do chores and get around town in the frailty index.

Correspondingly, other literature has confirmed that health factors such as obesity and hypertension, lifestyle factors such as physical and cognitive activity, and biological factors such as genetics, sex, and age influence individual memory trajectories in non-demented older adults (Elias, Goodell, & Dore, 2012; Hayes et al., 2015; Loprinzi & Frith, 2018; McFall, Wiebe, et al., 2015; Nyberg, Bäckman, Erngrund, Olofsson, & Nilsson, 1996; Olaya, Bobak, Haro, & Demakakos, 2017; Subramaniapillai et al., 2019). Additionally, memory may be also affected by age-related decline in other cognitive domains, such as speed or EF, due to declines in functional connectivity of multiple cortical networks (Shaw, Schultz, Sperling, & Hedden, 2015).

Speed. Speed of processing is perhaps one of the most basic facets of cognitive function and highly sensitive to age-related changes (Verhaeghen, 2013). In fact, the slowing of processing speed commonly occurs in older adults and influences the loss of cognitive function across other domains (Eckert, Keren, Roberts, Calhoun, & Harris, 2010; Harada, Natelson Love, & Triebel, 2013; Hertzog et al., 2003; Salthouse, 1996). Speed of processing involves coordinated activity across many neural networks. Therefore, normal age-related brain changes may have a cumulative effect which results in slowed speed across many tasks (Eckert, 2011; Eckert et al., 2010). For example, age-related loss of white matter integrity and myelination, as well as age-related reductions in hippocampal, prefrontal, and gray matter volume have all been linked to the slowing of processing speed (Chopra et al., 2018; Hong et al., 2015; Lu, Lee, et al.,

2011; Lu et al., 2013; Papp et al., 2014; Rosano et al., 2011). Normal age-related declines in speed begin as early as midlife and continue throughout the lifespan (Salthouse, 2009). Despite the generality of speed decline associated with normal or typical aging, there is substantial variability within speed performance and the rate of speed decline. For example, individuals within a non-demented population were shown to exhibit a wide range of speed performance and variability in speed decline over a nine-year period (McFall, Wiebe, Vergote, Anstey, & Dixon, 2015). Notably, speed may also be an indicator of preclinical cognitive decline (Bäckman, Jones, Berger, Laukka, & Small, 2005), and has also been reported to predict differences in mild cognitive impairment and the risk of AD (Christensen et al., 2005; Gorus, De Raedt, Lambert, Lemper, & Mets, 2008; Salthouse, 1996). Additionally, cognitive training focused on processing speed has been found to reduce the risk of dementia for non-demented, healthy older adults (Edwards et al., 2017). Taken together, processing speed is one of the most age-sensitive cognitive functions, considered to be one of the hallmarks of cognitive aging, and therefore a key cognitive domain for inclusion in this dissertation research.

Executive Function. EF encompasses higher-level cognitive processes required to make and execute plans, solve problems, set goals, shift between stimulus and response, and inhibit responses (e.g., Luszcz, 2012; West, 1996). EFs are thought to be among the most age-sensitive cognitive functions (de Frias, Dixon, & Strauss, 2009; Glisky, 2007; McFall et al., 2013; Raz, Dahle, Rodrigue, Kennedy, & Land, 2011) due to significant age-related neurodegeneration occurring in the prefrontal cortices (Raz & Rodrigue, 2006). Additionally, brain connectivity has also been found to be associated with EF (Bennett & Madden, 2014). For example, lower default mode network connectivity is associated with lowered performance on EF tasks in older adults (Andrews-Hanna et al., 2007; Damoiseaux et al., 2007). Similarly, longitudinal structural and

functional changes in brain connectivity have been associated with reductions in EF, with structural connectivity predicting age-related decline (Storsve, Grydeland, Sneve, Walhovd, & Fjell, 2016). Moreover, executive dysfunction is evident in normal aging, mild cognitive impairment, and in all stages of AD (Baudic et al., 2006; Harada et al., 2013; Swanberg, Tractenberg, Mohs, Thal, & Cummings, 2004). In fact, it was recommended that EF be examined over several measurements or timepoints in individuals with mild cognitive impairment due to AD, as deficits are commonly seen prior to AD clinical diagnosis (Albert et al., 2011). Specific to the variability in EF performance in normally aging populations, studies have found that non-demented older adults exhibit significant heterogeneity (Goh, An, & Resnick, 2012) in level of performance and rate of EF decline (McFall et al., 2013; Thibeau, McFall, Wiebe, Anstey, & Dixon, 2016). This variability in EF level and change can be attributed to a host of factors, including Type 2 diabetes, BMI, genetic influences, physical activity, frailty, and mobility impairment (Gross et al., 2016; Gunstad et al., 2007; McFall et al., 2013; McGough et al., 2011; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003; Thibeau et al., 2016; Yeung, Fischer, & Dixon, 2009).

Physical Frailty as Predictor of Cognitive Trajectories in Aging

Frailty is a heightened state of physical and health vulnerability, characterized by declines in physiological function across multiple systems (Chen, Mao, & Leng, 2014; Mitnitski, Fallah, Rockwood, & Rockwood, 2011). Prevalence rates of physical frailty vary dependent upon measurement instrument, geographical region, and age. Recent estimates suggest frailty rates of around 4% for older adults aged 50 – 54 but can range between 5 – 20% for those 65 years of age and older, depending on the population examined (Beard et al., 2016; Santos-Eggimann, Cuénoud, Spagnoli, & Junod, 2009). In Canada, prevalence rates of physical frailty in

community-dwelling adults between the ages of 54 and 74 is around 16%, rising to 52% at the age of 85 (Hoover, Rotermann, Sanmartin, & Bernier, 2013). Higher physical frailty has been associated with adverse health outcomes, such as falls, hospitalization, disability, as well as higher mortality risk (Blodgett, Theou, Mitnitski, Howlett, & Rockwood, 2019; Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Hoogendijk et al., 2017). Higher physical frailty is also associated with adverse cognitive outcomes such as cognitive decline, mild cognitive impairment, and AD (Boyle, Buchman, Wilson, Leurgans, & Bennett, 2010; Buchman, Boyle, Wilson, Tang, & Bennett, 2007; Kojima, Iliffe, & Walters, 2017; Rockwood et al., 2017). There are two main methods of measuring frailty in the literature: (a) the phenotypic model, and (b) the accumulation of deficits model. Each model has benefits and drawbacks in clinical practice and research. The phenotype model evaluates the presence or absence of five criteria: unintentional weight loss, exhaustion, weakness, slow gait, and low physical activity (Fried et al., 2001). According to this model, the presence of one or two of the criteria indicates a 'pre-frail' condition, and the presence of three or more indicates frailty. This model offers an advantage to clinicians, as each of the frailty components is easy to measure within a single clinical appointment (Cesari, Gambassi, Abellan van Kan, & Vellas, 2014). While this tool may offer a method for immediate stratification of individuals (Canevelli, Cesari, & van Kan, 2015), the predictive value, comprehensiveness, and clinical usefulness may be limited due to the small number of components (Cesari et al., 2014; Muscedere et al., 2016; Rockwood, Andrew, & Mitnitski, 2007).

The accumulation of deficits model is a comprehensive measure represented as a frailty index. The index is formed by the ratio of health deficits present in an individual to the total number of potential deficits measured (Rockwood & Mitnitski, 2007). Frailty indices have been

examined with anywhere between 20 – 70 items, but robust risk estimates have been found when 30 or more items are considered (Cesari et al., 2014; Mitnitski, Graham, Mogilner, & Rockwood, 2002; Mitnitski, Mogilner, & Rockwood, 2001). Notably, the deficits measured are not fixed; therefore, indices can include different sets of variables which represent the phenomena of frailty, and still produce similar relationship estimates across frailty indices ranging from between zero and one (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). While the continuous frailty index measure is not meant for describing separate and distinct categories of frailty, generally accepted cut-off points indicating varying levels of frailty have been identified in the literature. Specifically, FI scores of 0.00 – 0.12 indicate fit individuals, 0.12 – 0.24 are considered mildly frail or pre-frail, 0.25 – 0.36 are considered moderately frail, and scores over 0.36 are considered severely frail (Ambiàs-Novellas et al., 2018; Lansbury et al., 2017; Stow et al., 2018). Moreover, cut-off scores of 0.20 and 0.25 have been used to differentiate pre-frail from frail individuals (Dent, Kowal, & Hoogendijk, 2016; Searle et al., 2008). A score between 0.60 and 0.70 has been found to be the upper limit which indicates the addition of another health deficit would likely result in mortality (Rockwood & Mitnitski, 2006, 2011). As the calculation of a frailty index requires measurement of multiple deficits, this approach entails a comprehensive assessment and may present barriers for ease of use in a clinical setting (Cesari et al., 2014; Rockwood et al., 2005). However, the information needed for the frailty index may already be present in health records (Rockwood & Mitnitski, 2007). Additionally, the benefits offered from the ability to (a) obtain a continuous measure of frailty, (b) depict health trajectories across time, and (c) have better predictive value from a higher number of deficits (compared with the phenotype model) may outweigh any additional time investment necessary to establish the

initial frailty score (Cesari et al., 2014; Pérez-Zepeda, Cesari, & García-Peña, 2016; Shi et al., 2018).

In the current research, we use the frailty index (see Table 2-3) for four main reasons: (a) the frailty index shows greater predictive value than the frailty phenotype model for populations in community settings (Theou et al., 2015), (b) it is considered one of the most robust frailty assessment tools (Dent, Kowal, & Hoogendijk, 2016), (c) it is unidimensional and has high construct validity (Widagdo, Pratt, Russell, & Roughead, 2016), and (d) the total frailty index score (more than individual health deficits) has been found to be a more sensitive predictive of adverse outcomes (Rockwood & Mitnitski, 2007).

Cognitive deficits are often considered as a part of frailty indices; however, frailty and cognitive decline are two distinct constructs that may co-occur and interact in old age (Robertson, Savva, & Kenny, 2013). Most of the cognition-frailty literature examines declines in global cognition, but recently frailty has been associated with specific cognitive declines in EF and speed (Armstrong, Mitnitski, Launer, White, & Rockwood, 2013; Langlois et al., 2012; Mitnitski et al., 2011; Rolfson et al., 2013). Additionally, frailty increases risk of adverse brain and cognitive outcomes, including decline and dementia (Beard et al., 2016; Kojima, Taniguchi, Iliffe, & Walters, 2016; Song, Mitnitski, & Rockwood, 2011). For example, pre-frail and frail individuals in the English Longitudinal Study of Ageing had a higher risk of developing dementia than non-frail individuals (Rogers, Steptoe, & Cadar, 2017). Recently, Wallace and colleagues (2019) found that frailty moderated the relationship between AD pathology and expression. Specifically, individuals with low frailty were able to tolerate AD pathology, whereas highly frail individuals were more likely to have more AD pathology and clinical

expression as AD. Taken together, the evidence indicates a strong link between frailty and cognitive decline and impairment.

Mobility as Predictor of Cognitive Trajectories in Aging

Mobility is a key component of functional health for older adults, strongly linked to independence and quality of life (Davis et al., 2015; World Health Organization, 2015). Mobility disability, one of the most common disabilities for older adults, represents a functional state whereby walking speed and balance are impaired, causing difficulties with everyday activities (Satariano et al., 2014; World Health Organization, 2015). This disability results from age-related deterioration in several physiological systems, including the central nervous system, skeletal muscles, joints, and sensory systems (Ferrucci et al., 2016). Prevalence rates of mobility impairment in adults over the age of 65 vary depending on the population examined (Courtney-Long et al., 2015; He & Larsen, 2014). In Canada, 20% of those aged 65 and over have mobility impairments that affect their day to day lives (Bizier, Fawcett, & Gilbert, 2016). Age-related mobility impairment has been associated with an increased risk of disability, social isolation, increased risk of falls, loss of independence, institutionalization, and mortality (Ferrucci et al., 2016; Mänty et al., 2010; Newman et al., 2006; Rosso, Taylor, Tabb, & Michael, 2013; Webber, Porter, & Menec, 2010). Additionally, mobility impairment has a strong link to cognition and has been associated with cognitive decline, impairment, and dementia (Borges, Radanovic, & Forlenza, 2018; Montero-Odasso et al., 2015).

Mobility has been closely related to cognition across several domains including memory, speed, and EF (Berryman et al., 2013; Christensen, Mackinnon, Korten, & Jorm, 2001; Desjardins-Crépeau et al., 2014; Doi et al., 2014; Eeles & Choy, 2015; Verghese, Wang, Lipton, Holtzer, & Xue, 2007). Notably, age-related mobility decline accelerates between the ages of 60

and 70, with a wide range of heterogeneity between individuals, and differing trajectories between males and females (Ferrucci et al., 2016). Age-related decline occurs in multiple systems and brain regions (i.e., central nervous system, neuromotor responses, prefrontal cortex, and visuospatial brain regions) that contribute to mobility (Eeles & Choy, 2015). In addition to the motor cortex and the cerebellum, the prefrontal cortex is involved in the planning and execution of mobility, indicating that brain regions for cognitive function and mobility are overlapping. In fact, a common mechanism is postulated to be the cause of co-occurring mobility and cognitive decline (Hausdorff & Buchman, 2013; Montero-Odasso, Verghese, Beauchet, & Hausdorff, 2012).

Decline in gait speed precedes cognitive decline in healthy older adults and has been associated with EF decline irrespective of cognitive impairment (Callisaya et al., 2015; Camicioli, Howieson, Oken, Sexton, & Kaye, 1998; Ojagbemi et al., 2015). Furthermore, the slowing of gait speed has been found several years prior to the onset of neurocognitive disorders and incident dementia (Camicioli et al., 1998; Dumurgier et al., 2016; Kuate-Tegueu et al., 2017; Ojagbemi et al., 2015; Parodi et al., 2018). In a recent meta-analysis of longitudinal studies, slow baseline gait speed was found to predict cognitive decline and dementia, indicating that physical impairment is a core factor in cognitive decline (Kikkert, Vuillerme, van Campen, Hortobágyi, & Lamoth, 2016).

Frailty and mobility have been identified as distinct but related constructs. Mobility impairment occurs at a high level of frailty and is one of multiple factors that are included in frailty measures. However, mobility impairment is not enough to identify frail individuals (Davis, Rockwood, Mitnitski, & Rockwood, 2011; Eeles & Choy, 2015). Additionally, mobility has been identified as a predictor of incident frailty as well as frailty transition states; better

mobility is associated with stability or improvement in frailty status (Fallah et al., 2011; Rothman, Leo-Summers, & Gill, 2008). Notably, it is possible that not all mobility-impaired or frail individuals experience cognitive decline or dementia, indicating some individuals may be resilient to the effects of these physical health adversities on cognition. An emerging area of research, cognitive resilience, seeks to understand preservation of cognitive performance and capacity despite risk profiles for decline and impairment.

Cognitive Resilience: An Indicator of Healthy Brain Aging?

Resilience is a concept long applied in psychology, indicating an ability to adapt and maintain well-being in the face of adversity (Anstey & Dixon, in press). Resilient aging is thought to be examined from a salutogenic approach (a health promotion approach) rather than focusing on the pathology of aging and neurodegenerative diseases. A salutogenic approach offers avenues to examine antecedents or predictors of resilience in older adults along a continuum of health and wellness (Hicks & Conner, 2014).

The concept of resilient aging has been examined in a variety of different ways, conceptualizing many facets of human existence and experience, such as emotional and psychological resilience. For example, psychological resilience in aging has been quantified by characteristics such as emotional regulation, self-efficacy, greater social support, low neuroticism, greater life satisfaction, higher use of proactive coping strategies, a high use of humour, and a growth mindset (Fontes & Neri, 2015). Recently, the concept of resilient aging has been conceptualized through biological attributes. For example, physical resilience has been defined as a "characteristic at the whole person level which determines the individual's ability to resist functional decline or recover physical health following a stressor" (p. 493) and has been indicated as an integral part of successful aging (Whitson et al., 2016).

When applied to cognitive aging, the emerging construct of resilience can be defined as an ability to maintain cognitive function despite the presence of adversities significantly associated with decline, impairment, and dementia. Such adversities come from a variety of domains including genetic, functional health, lifestyle, biological, and sociodemographic. Recent research has examined cognitive resilience to certain risk factors, such as *APOE* ε4 genetic risk, and AD neuropathology (Arnold et al., 2013; Kaup et al., 2015). This emerging research highlights a unique and measurable concept – cognitive resilience, which suggests that even with major risk profiles for the neurodegenerative disease, some individuals may be relatively spared from cognitive impairment (Kaup et al., 2015; McDermott et al., 2017).

Examining cognitive resilience to adversities associated with cognitive decline, impairment, and dementia fosters the opportunity to identify potential predictive profiles of resilient and non-resilient individuals. For example, Kaup and colleagues (2015) examined cognitive resilience to *APOE* genetic risk as stratified by race. Resilience was classified as relatively stable MMSE scores across a timespan of eleven years despite *APOE* risk (ε4+) status. Their results indicated that cognitive resilience was predicted by differing factors for black and white older adults. Specifically, for black older adults, resilience was predicted by a high literacy level, high education, female sex, and an absence of diabetes. In contrast, for white older adults, cognitive resilience was predicted by having no negative life events, a high literacy level, older age, high education, and time spent reading.

McDermott and colleagues (2017) found that predictors of memory resilience to *APOE* genetic risk differed for men and women. While there were similar predictors for both males and females, several predictors were unique to women (e.g., PP, volunteering, subjective health). Therefore, resilience may be a relational construct, in that it may vary according to the

constellation of individual factors (e.g., sex) or resources available (e.g., subjective health). Additionally, the resources (or protective factors) available may vary within an individual across time (Staudinger & Greve, 2016). This is important for research in brain and cognitive aging because, from a lifespan developmental perspective, a basic tenet of human aging is modifiability (Staudinger & Greve, 2016). Understanding the circumstances that provide the best context for modifying resilience could provide insight for exogenous conditions aimed at risk-reduction and maintenance of cognitive function (Staudinger & Greve, 2016). Simply, the more we understand about the developmental conditions which underlie a resilient response, the more effective interventions may be at protecting cognitive health in the face of vulnerability (Lavretsky, 2014; Staudinger & Greve, 2016).

Potential Predictors of Cognitive Resilience to Frailty and Mobility Risk

As previously established, several lifestyle, demographic, and genetic factors may contribute (either positively or negatively) to cognitive resilience (Kaup et al., 2015; McDermott et al., 2017). The following paragraphs discuss the major risk and protective factors proposed for examination in Chapters Three and Four of this dissertation research. All of these factors have been previously associated with cognitive impairment, decline, and dementia. These factors may be modifiable or non-modifiable, and some factors are conversely related. For example, social engagement is protective, while social isolation is a risk factor (Dixon & Lachman, 2019). Informed by recent VLS research (i.e., McDermott et al., 2017; McFall et al., 2019), 13 core (common across Chapters Three and Four) and nine additional factors (unique to Chapter Four) have been chosen for examination as potential predictors of cognitive resilience (see Tables 1-1 and 1-3 for a comparison of the predictors across studies). These 22 factors have been clustered into four broad domains: demographic, health (including functional health), lifestyle, and genetic

(see Table 1-2; McDermott et al., 2017; McFall et al., 2019). The 13 core predictors used in both Chapters Three and Four are age, sex, marital status, living status, pet ownership, education, social activity, cognitive activity, volunteer activity, alcohol use, smoking, *APOE* and *BDNF* genetic status. The additional factors unique to Chapter Four are physical activity, BMI, diabetes, peak flow, grip strength, depressive symptoms, subjective health, anti-inflammatory medication, and PP (see Table 1-2).

Demographic factors. Several demographic factors have been associated with differential trajectories of cognitive aging, including age, sex, education, marital status, living status, and pet ownership.

Age. The 'greying of the population' is a worldwide phenomenon that will continue for several decades. In Canada, by 2021, the number of adults over the age of 65 will outnumber children under the age of 14 (Statistics Canada, 2015). Higher age has been associated with lower cognitive performance and steeper decline in non-demented older adults across several domains (Hoogendam, Hofman, van der Geest, van der Lugt, & Ikram, 2014; McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016). Although cognitive impairment and dementia are not normal conditions of aging, increasing age is the foremost risk factor for AD. In fact, the risk for AD doubles every five years after the age of 65 (Alzheimer's Society, 2010).

Sex. Sex differences have been noted in non-demented cognitive performance and cognitive trajectories across several studies (McCarrey et al., 2016; Munro et al., 2012). For example, males have been found to outperform females on baseline measures of visuospatial ability, but females were found to outperform males on baseline memory, EF, perceptuomotor speed, and language tasks (McCarrey et al., 2016). Regarding clinical status, females are at a higher risk for developing non-amnestic mild cognitive impairment and AD (Au, Dale-McGrath,

& Tierney, 2017; Riedel, Thompson, & Brinton, 2016). Specifically, the prevalence of AD is higher for females, the clinical manifestation and progression of the disease differs for males and females, and females have lower cognitive performance than men in similar stages of AD (Laws, Irvine, & Gale, 2016; Pike, 2017).

Education. Education is known to influence cognitive decline, impairment, and AD. Higher education confers protection, while lower education is a risk factor for developing impairment and dementia (Sattler, Toro, Schönknecht, & Schröder, 2012). For example, recently higher education has been associated with higher rates of cognitive function and slower rates of cognitive decline in a cohort of older Danish adults without cognitive impairment at baseline (Foverskov et al., 2018). This beneficial cognitive effect may occur through increasing cognitive reserve, which reduces risk of clinical impairment (Lenehan, Summers, Saunders, Summers, & Vickers, 2015; Thow et al., 2017). In fact, higher educational attainment has been associated with decreased risk of AD across several studies, including a recent meta-analysis (Meng & D'Arcy, 2012; Xu et al., 2015).

Other factors that have been found to confer protection against cognitive decline include being married, living with someone, and owning pets (Enders-Slegers & Hediger, 2019; Kotwal, Kim, Waite, & Dale, 2016; Mousavi-Nasab, Kormi-Nouri, Sundström & Nilsson, 2012). For example, being married has been found to be positively associated with memory performance and memory decline (Mousavi-Nasab et al., 2012). In contrast, being single has been associated with a higher risk of cognitive decline and impairment across several samples (Feng et al., 2014; Wu, Lan, Chen, Chiu, & Lan, 2011). Living status has been found to be linked to cognitive, social, and health factors. For example, living alone has been found to increase the risk for dementia and negative health outcomes such as poor functional health, and multiple falls

(Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Kharicha et al., 2007). Additionally, older males living alone experienced a more rapid cognitive decline than their married counterparts (van Gelder et al., 2006). Pet ownership and human-animal interaction have been found to be related to several positive health factors, such as increased physical activity, social activity, cognitive function, psychological health, and decreased loneliness (Friedmann et al., 2020; Knight & Edwards, 2008; Matchock, 2015; Toohey, McCormack, Doyle-Baker, Adams, & Rock, 2013). Additionally, human-animal interaction has been found to increase MMSE scores in older adults with dementia (Moretti et al., 2011). Therefore, pet ownership may provide an avenue for cognitive protection and fostering cognitive resilience.

Genetic Factors. Genetic factors contribute to the interindividual variability of cognitive aging, possibly accounting for up to 60% of the variability in general cognitive function in later life (Harris & Deary, 2011; Laukka et al., 2013). Notably, the influence of genetics on cognitive function increases across the lifespan and differs according to clinical status (Pedersen & Gerritsen, 2015; Plomin & Deary, 2014). While many genetic variants have been associated with cognitive decline and impairment, two genetic factors (i.e., *APOE*, rs7412 and rs429358; *BDNF*, rs6265) have been selected for this dissertation because of their previous associations with frailty, mobility, and cognitive function (Barha, Best, Liu-Ambrose, & Rosano, 2018; Thibeau et al., 2016; Thibeau et al., 2017).

Apolipoprotein. APOE is a lipoprotein involved in lipid metabolism and transportation. The *APOE* gene has three allelic variations, ε2, ε3 and ε4, yielding six possible genotypes: ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4 and ε4ε4 (Lahiri, Sambamurti, & Bennett, 2004). *APOE* has been associated with multiple trajectories and clinical outcomes of aging, including normative cognitive decline, MCI, and AD (Brainerd, Reyna, Petersen, Smith, & Taub, 2011; Small,

Rosnick, Fratiglioni, & Backman, 2004; Wisdom, Callahan, & Hawkins, 2011). The risk for AD increases according to the *APOE* genotype, such that *APOE* ε2 may be relatively protective, ε3 is neutral (neither risk increasing nor protective), and ε4 increases the risk substantially (Corder et al., 1993; Lahiri et al., 2004). Regarding cognitive performance, ε4 carriers have been shown to perform significantly worse than ε4 non-carriers on measures of cognitive functioning, including memory, speed, and EF (Wisdom et al., 2011). *APOE* ε4 has been classified as a "frailty gene" due to its association with differential mortality in older adults (Gerdes, Jeune, Ranberg, Nybo, & Vaupel, 2000). *APOE* ε4 has also been associated with more rapid decline in gait speed, and less cognitive resilience to AD neuropathology (Buchman et al., 2009; Negash, Xie, et al., 2013).

Brain-Derived Neurotrophic Factor. BDNF is highly expressed in the nervous system and is involved in several brain functions including neuronal growth, differentiation, repair and survival (Bathina & Das, 2015). A substitution of valine by methionine at codon 66 (the Met allele) in the single nucleotide polymorphism of the *BDNF* gene (rs6265) has been linked to disrupted neuronal processing, resulting in a decreased availability of BDNF (Egan et al., 2003). Additionally, low levels of brain and plasma BDNF expression and circulation have been linked to functional impairment, frailty, cognitive decline, MCI, and AD pathology (Buchman et al., 2016; Erickson, Miller, & Roecklein, 2012; Inglés et al., 2016; Navarro-Martínez et al., 2015; Shimada et al., 2014). Conversely, high levels of BDNF in plasma have been linked to a lowered risk for MCI and AD (Lau, Ludin, Rajab, & Shahar, 2017; Weinstein et al., 2014). Notably, BDNF has recently been identified as a potential neural mediator of resilience, through its role of facilitating adaptive neuroplasticity (Karatsoreos & McEwen, 2013; Rothman & Mattson, 2013). However, the association between the *BDNF* Val66Met polymorphism and cognitive function is unclear, as several studies have conflicting results. A recent review by Toh and colleagues

(2018) examined the association between the Val66Met polymorphism and cognitive function across several cognitive domains in both clinical and non-clinical status populations. Their review indicated that although several studies have consistently indicated an association between the *BDNF* gene and cognitive function, these studies indicated positive associations for differing alleles. For example, several studies found positive effects on cognition for Val/Val carriers, while others found similar effects for Met carriers. They concluded the positive effect of the Met allele had not be consistently established and may occur only in tandem with certain disease states in which BDNF expression and circulation is affected (Toh, Ng, Tan, Tan, & Chan, 2018). Taken together, the influence of *BDNF* on cognition or on cognitive resilience might be more apparent when certain physiological disease states or deficits are present, such as frailty or low mobility.

Lifestyle factors. Lifestyle factors influencing cognitive function in aging include social activity, cognitive activity, physical activity, volunteer activity, alcohol use, and smoking (Anstey, 2014; Marioni et al., 2015; Middleton, Barnes, Lui, & Yaffe, 2010). In fact, a randomized control trial indicated that higher levels of social, cognitive, and physical activity were associated with higher cognitive performance on a neuropsychological test battery, and with higher performance in EF and speed domains of cognition (Ngandu et al., 2015).

Social Activity. Social activity is a core component of successful aging and has been found to be strongly associated with quality of life, physical health, cognitive performance, and reduced risk of cognitive decline (Cherry et al., 2013; Douglas, Georgiou, & Westbrook, 2017; Hajek et al., 2017; Tomioka, Kurumatani, & Hosoi, 2016; Weber, 2016). In contrast, social isolation has been identified as a major risk factor for poor health, reduced sense of well-being, higher mortality rates, increased risk for vascular diseases, cognitive decline, and dementia

(Courtin & Knapp, 2017; Friedler, Crapser, & McCullough, 2015; Holt-Lunstad, Smith, & Layton, 2010). For example, a recent review of longitudinal studies indicated that social isolation is associated with higher risk of dementia (Kuiper et al., 2015).

Notably, the risk of social isolation increases as functional status decreases. For example, the slowing of gait speed has been associated with an increase in social isolation, and increased scores on a frailty index have been associated with decreased social engagement in Canadian older adults (Andrew & Keefe, 2014; Shankar, McMunn, Demakakos, Hamer, & Steptoe, 2017; Warren, Ganley, & Pohl, 2016). As such, high social engagement may foster cognitive resilience in individuals who are frail or have low mobility.

Cognitive Activity. Cognitive training and several types of cognitive activity have been found to be associated with cognitive performance in non-clinical and clinical populations (Bherer, 2015; Hertzog, Kramer, Wilson, & Lindenberger, 2008; Hyer et al., 2016; Lampit, Valenzuela, & Gates, 2015; Park & Bischof, 2013). For example, a recent review has found that cognitive training improves domain-related cognitive performance in non-demented older adults (Butler et al., 2018). In 2016, Hyer and colleagues reported that two computer-based programs targeting working memory improved performance for individuals with MCI. Additionally, individuals with early-stage AD have been shown to benefit from a cognitive training task (Cavallo, Zanalda, Johnston, Bonansea, & Angilletta, 2016). These cognitive benefits may remain domain-specific with little transfer to general cognitive function (Sala & Gobet, 2019), but have been shown to be relatively stable for prolonged periods in multiple studies (Cavallo et al., 2016; Dahlin, Nyberg, Bäckman, & Neely, 2008; Park & Bischof, 2013).

Cognitive interventions have been associated with improvements in mobility and cognitive-related outcomes (Marusic, Verghese, & Mahoney, 2018; Ross, Sprague, Phillips,

O'Connor, & Dodson, 2016; Smith-Ray et al., 2013; Verghese, Mahoney, Ambrose, Wang, & Holtzer, 2010). Additionally, Ng and colleagues (2015) found that a cognitive intervention reversed frailty scores. Moreover, it has been recommended that cognitive assessments be used when assessing risk of adverse outcomes for frail adults, as cognitive impairment in the presence of frailty indicates higher risk for adverse outcomes. Taken together, high cognitive activity could be a potential predictor of cognitive resilience in older adults who are frail or mobility impaired.

Physical Activity. Physical activity is defined as any skeletal muscle movement that results in energy expenditure (Caspersen, Powell, & Christenson, 1985). Physical activity encompasses a broad range of activities, (e.g., walking, aerobic exercise) and can range from light to vigorous intensity. While moderate to vigorous intensity exercise is known to be cognitively beneficial (Erickson, Hillman, & Kramer, 2015), increasing evidence supports everyday or leisure physical activity as a more accessible avenue for influencing brain and cognitive health for older adults (Thibeau et al., 2016; Thibeau et al., 2017; Willey et al., 2016). For example, in a sample of non-demented older adults, higher levels of everyday physical activity were found to be associated with better EF performance, and less EF decline over time (Thibeau et al., 2016). Moreover, Willey and colleagues (2016) indicated that low levels of low-intensity physical activity were associated with cognitive decline across EF, memory, and speed domains in non-demented older adults. Regarding cognitive impairment, greater levels of daily physical activity have been associated with a decreased risk of Mild Cognitive Impairment (MCI), and AD (Covell et al., 2015).

Notably, while some individuals who are frail may also have low levels of physical activity, there is a substantial amount of variability in activity level (Huisingh-Scheetz et al.,

2018). Additionally, leisure physical activity interventions may improve health status of mobility-impaired older adults (Crawford, Hollingsworth, Morgan, & Gray, 2008). A recent review indicated that physical activity has been found to consistently improve cognitive performance in older frail adults (Landi et al., 2010). Moreover, poor physical function (including mobility) and physical inactivity are predictors of faster rates of cognitive decline (Zaninotto, Batty, Allerhand, & Deary, 2018). Taken together, it is possible that physical activity may be a predictor of cognitive resilience to frailty and low mobility.

Volunteer Activity. Volunteering is a promising lifestyle activity thought to have beneficial effects on cognitive function for older adults (Guiney & Machado, 2018; Proulx, Curl, & Ermer, 2018). Volunteering has been found to be beneficial to working memory and speed (Proulx et al., 2018), and mitigate cognitive decline and risk for impairment (Gupta, 2018; Infurna, Okun, & Grimm, 2016). A recent review has suggested that this benefit may come from increases to physical and social activity, and cognitive stimulation which could have a positive influence on neurological and mental health (Guiney & Machado, 2018).

Alcohol Use. Alcohol consumption is widespread in Canada. Recent surveys have indicated that 77% of people over the age of 18 have consumed alcohol within the past year (Statistics Canada, 2017). Studies examining the association between cognitive function and alcohol use have mixed results. The majority of studies suggest an inverted u-shaped relationship between alcohol consumption and cognitive function. These findings indicate that low and moderate use is associated with protective effects against cognitive decline, yet heavy drinking is associated with higher risk of cognitive decline and dementia (Anstey, Mack, & Cherbuin, 2009; Carrigan & Barkus, 2016; Piumatti, Moore, Berridge, Sakar, & Gallacher, 2018; Sachdeva, Chandra, Choudhary, Dayal, & Anand, 2016). However, recent studies have suggested the

protective effect could be due to confounding factors such as socioeconomic status, education, or abstainer bias (Hassing, 2018; Topiwala et al., 2017; Topiwala & Edmeier, 2018). Adding to this complexity, alcohol use was a significant predictor of resilience to *CLU* genetic risk for females (McDermott et al., 2017), indicating the effect of alcohol on cognitive function may depend on other factors, such as risk for AD. Considering this evidence, alcohol use (yes or no) was included as a predictor of resilience to frailty in the present reserach.

Smoking. Cigarette smoking increases the risk for major diseases such as coronary heart disease, lung cancer, and stroke, and is the leading preventable cause of death in Canada (Center for Disease Control and Prevention, 2013; Rhem, Baliunas, Brochu, & Fischer, 2006). Smoking has been linked to cognitive impairment and decline (Okusaga et al., 2013). In fact, smoking has recently been linked to long-term deficits in EF and memory, and current smoking increases the risk for EF impairment when compared to former smokers (Amini, Sahil, & Ganai, 2020). Smoking has also been associated with deficits in processing speed and global cognitive function for females (Zaninotto, Batty, Allerhand, & Deary, 2018).

Health factors. Health factors (including health conditions and markers of functional health) contribute substantially to the variability in cognitive trajectories (Institute of Medicine, 2015). While many disease states and functional health biomarkers have been associated with cognitive decline and impairment, nine factors (i.e., diabetes, depressive symptoms, subjective health, anti-inflammatory medication use, peak flow, grip strength, BMI, and PP) have been selected for consideration in the fourth chapter of this dissertation because of their previous associations with cognitive resilience, mobility, and/or cognitive performance across the three domains (Caballero, McFall, Wiebe & Dixon, 2020; McDermott et al., 2017; McFall et al., 2019).

Diabetes. Type 2 diabetes has been established as a major risk factor for cognitive decline and dementia (Livingston et al., 2017; Livingston et al., 2020). Recently, diabetes has been associated with decline in verbal memory and fluency in non-demented older adults over a period of five years (Callisaya et al., 2018). Furthermore, diabetes has been linked to lower EF performance, lower global cognition scores, lower episodic memory performance, slower processing speed, and lower verbal abilities in older adults of various cognitive status (Marseglia et al., 2017; Palta et al., 2017; Sadanand, Balachandar, & Bharath, 2016). Mechanistically, diabetes may contribute to cognitive decline through cortical atrophy, increased accumulation of beta-amyloid, structural damage such as white matter hyperintensities, and functional impairment of brain cells and nerves (Lee et al., 2018; Mankovsky, Zherdova, van den Derg, Biessels, & Bresser, 2018; Moran, Beare, Wang, Callisaya, & Srikanth, 2019).

Peak Expiratory Flow. Pulmonary function declines with age and is often measured by either a peak flow meter or a spirometer, which assess parametric indicators of lung function. Peak expiratory flow has been associated with a variety of outcomes for older adults, including lower mobility (walking speed), lower quality of life, higher rates of functional disability, hospitalization, and mortality (Finkel, Bravell, & Pedersen, 2020; Roberts & Mapel, 2012; Trevisan et al., 2020). It is thought that inadequate oxygenation may cause brain atrophy and structural changes which affect cognitive performance (Ferreira, Tanaka, Santos-Galduróz, & Galduróz, 2015). While a number of studies have suggested a link between pulmonary and cognitive function, a recent systematic review of longitudinal studies has found inconsistency in the relationship between pulmonary function and cognitive performance in older adults, highlighting the need for further rigorous longitudinal research (Duggan et al., 2020).

Grip Strength. Hand grip strength is a measure of overall body strength (Neumann, Kwisda, Krettek, & Gaulke, 2017; Wearing, Konings, Stokes, & de Bruin, 2018). Grip strength is an age-dependent process, thought to be a marker of biological vitality, and has significant associations with cognitive performance (Zammit et al., 2018). In fact, a recent study by Sternäng and colleagues (2016) found longitudinal relationships between grip strength and verbal abilities, processing speed, memory, and spatial abilities. Additionally, higher hand grip strength is associated with lower risk for cognitive decline and impairment (McGrath et al., 2020). Furthermore, McDermott and colleagues (2017) found that grip strength was a predictor of memory resilience in non-demented older adults.

BMI. Higher BMI in mid-life has been identified as one of the top risk factors for cognitive decline and impairment (Anstey et al., 2011; Livingston et al., 2017). The relationship is complex, however, with some studies showing that elevated BMI in late life is linked to decreased risk for cognitive impairment (Emmerzaal, Kiliaan, & Gustafson, 2015). Specifically, Bohn and colleagues (2020) found that elevated BMI was associated with less cognitive decline in the domains of EF, memory, and neurocognitive speed for non-demented, community-dwelling older females. In contrast, Caballero and colleagues (2020) found that lower BMI was an important predictor of membership in a class of individuals characterized by high-and-stable EF performance over time compared with a class of individuals with lower performance and declining EF. Therefore, there is a need to clarify the conditions under which BMI influences cognitive trajectories in later life. Recently, BMI has been investigated in relation to cognitive resilience. Specifically, McDermott and colleagues (2017) found that lower BMI was a predictor of memory resilience to AD genetic risk, but only for female carriers. Taken together, current

evidence suggests that the relationship between BMI, cognition, resilience, and aging is complex and needs further examination.

Pulse Pressure. Pulse pressure (PP), a proxy measure of arterial stiffness, is measured as the difference between systolic minus diastolic blood pressure (McFall et al., 2015). PP increases with age (Raz et al., 2011), and elevated PP is associated with a compromised blood brain barrier, neuroinflammation, and neurodegeneration (Levin, Carnegie, & Celermajer, 2020). Notably, PP has been associated with many cognitive outcomes, including cognitive stability, cognitive decline, and AD neuropathology (Caballero, McFall, Wiebe, & Dixon, 2020; Hughes et al., 2013; McFall et al., 2015; Sha, Cheng, & Yan, 2018). For example, when distinguishing between subclasses of individuals based on EF performance and change, Caballero and colleagues (2020) found that lower PP was a predictor of membership in the highest level and stable EF performance class, indicating that individuals with lower PP had high EF levels and stable EF performance over time. However, the relationships between PP and cognition may be dependent on other factors, such as a lower initial systolic blood pressure, genetic status, or biological sex (McDade et al., 2016; McDermott et al., 2017; Nation et al., 2016). For example, relative to cognitive resilience, McDermott and colleagues (2017) found that PP was an important and genetically robust predictor of memory resilience for older non-demented females, but not for males. Therefore, PP may be uniquely predictive of cognitive resilience and could be dependent on the adversity or the cognitive domain examined.

Depressive Symptoms. Depression is a common mental health condition affecting 2 – 15% of older adults (Beekman, Copeland, & Prince, 1999; Kok & Reynolds, 2017). Late-life depression has been associated with impaired social functioning, poor medical outcomes, increased risk of mortality, and faster cognitive decline (Donovan et al., 2017; Gallo et al., 2013;

Ganguli, Dodge, & Mulsant, 2002). A systematic review and meta-analysis indicated that depressed individuals had impairments in cognitive domains of EF, memory, and attention (Rock, Roiser, Reidel, & Blackwell, 2013). Additionally, high and increasing depressive symptoms are linked to a higher risk for dementia (Kaup, Byers, & Falvey, 2016). Depression has also been found to have a bidirectional relationship with frailty, as frail individuals are more likely to have higher depressive symptoms than non-frail individuals (Soysal et al., 2017). Additionally, the absence of depressive symptoms has been found to be a predictor of cognitive resilience to AD genetic risk (McDermott et al., 2017). Therefore, the presence of depressive symptoms (yes or no) has been included as a predictor of resilience.

Subjective Health. Healthy aging may be operationalized through self-rated health measures, which have been consistently associated with activities of daily living and disability (Fiacco, Mernone, & Ehlert, 2020; Fong & Kok, 2020). According to research, there is a disconnect between objective health status and subjective reports or self-rated health. Specifically, older adults report high levels of health despite clinical health status or number of chronic conditions (Idler & Benyamini, 1997; Tkatch et al., 2017). Taking this discrepancy into consideration, self-perception of health may be an indicator of resilience. In fact, subjective health was found to be a predictor of resilience to genetic risk for AD (McDermott et al., 2017). Therefore, subjective health is included as a potential predictor of cognitive resilience.

Anti-Inflammatory Medication. Anti-inflammatory medications (i.e., members of a drug class that reduces pain, decreases fever, and decreases inflammation) are the most prescribed medication for pain management in older adults (Abdulla et al., 2013). While associated with several adverse health events (e.g., gastrointestinal issues, cardiovascular issues, and bleeding complications), beneficial effects of use have been found on cognitive function and reducing the

risk of dementia (Nevado-Holgado et al., 2016; Pilotto et al., 2003; Szekely et al., 2008; Wongrakpanich, Wongrakpanich, Melhado, & Rangaswami, 2018; Zandi et al., 2002; Zhang et al., 2018). Additionally, McDermott and colleagues (2017) found that anti-inflammatory medication was predictive of resilience to AD genetic risk for females, therefore, it was also included in the present research.

In summary, 13 core predictors will be used in Chapters Three and Four. Specifically, these 13 predictors are from three domains (i.e., genetic, demographic, and lifestyle) and include *APOE* genetic status, *BDNF* genetic status, sex, age, education, marital status, living status, pet ownership, alcohol use, smoking, cognitive activity, volunteer activity, and social activity. Additionally, nine predictive factors are considered for inclusion in the cognitive resilience to mobility chapter physical activity, depressive symptoms, anti-inflammatory medication use, self-rated overall health, diabetes, BMI, PP, peak expiratory flow, and grip strength. These additional factors are already included in the frailty index and therefore are not being considered for inclusion as separate variables in Chapter Three.

Section Three: Thematic Integration in Three Proposed Studies

Three Programmatic Studies: Goals and Procedures

The overall goal of this dissertation is to augment and inform the emerging frailty, mobility, and cognitive resilience literature via three novel and significant studies. Participants for these studies came from the Victoria Longitudinal Study (VLS). the VLS is a large-scale, longitudinal examination of aging that has been well-described elsewhere (Dixon & deFrias, 2004). The samples used for these studies are described in each chapter.

Chapter Two: The first longitudinal study is entitled “Frailty Effects on Non-Demented Cognitive Trajectories are Moderated by Sex and Alzheimer’s Genetic Risk.” This chapter has

recently been published in a peer-reviewed journal and is summarized here (Thibeau, McDermott, McFall, Rockwood, & Dixon, 2019). The full version including references appears in Appendix A. It establishes the effects of frailty on cognitive performance (level) and change (slope) in three cognitive domains and examines moderation of these frailty-cognition associations by two major risk factors associated with AD (i.e., sex and *APOE* genetic risk). Specifically, this chapter examines the relationships of both level (at a statistical centering age) and slope (longitudinal change) between frailty and three cognitive domains: (a) episodic memory, (b) neurocognitive speed, and (c) EF as moderated by two non-modifiable risk factors for AD (i.e., sex and *APOE* genetic risk). For Chapter Two, a three-wave dataset was assembled from the Victoria Longitudinal Study (VLS), covering a 40-year age span (53–95). After exclusionary criteria were applied, the participant sample was comprised of non-demented community-dwelling older adults who had provided biofluid for genotyping between 2009 and 2011 (n = 632). Structural equation modeling was used to investigate three research goals. Specifically, confirmatory factor analysis, longitudinal measurement invariance, latent growth modeling, and moderation analysis were conducted using Mplus 7 (Muthén & Muthén, 1998).

The aim of Research Goal One (RG1) was to examine how frailty (level or change) affected the level and change in the three latent cognitive variables. The aim of Research Goal Two (RG2) was to examine whether *APOE* (risk, non-risk) moderated the level and longitudinal frailty-cognition relationships. Finally, the aim of Research Goal Three (RG3) was to examine whether sex moderated the level and longitudinal frailty-cognition relationships.

Four main results were produced. First, frailty levels predicted speed and EF performance (level) and differential memory change slopes. Second, change in frailty predicted the rate of decline for both speed and EF. Third, the sex moderation analyses indicated that females were

sensitive to: (a) frailty effects on memory change and (b) frailty change effects on speed change. In contrast, the frailty effects on EF change were stronger in males. Fourth, the genetic moderation analyses showed that *APOE* risk (e4+) carriers were selectively susceptible to frailty effects on memory change. This chapter provides a novel contribution as it presented evidence of how frailty in older adults affected performance and change across three age-sensitive domains of cognition. Additionally, it was among the first to contribute information of how these frailty-cognition relationships are modified by two non-modifiable AD biomarkers. Moreover, these novel results provide the groundwork for study two.

Chapter Three: The second longitudinal study is entitled "Cognitive Resilience to Frailty: Definition and Determinants of Protective Profiles". The overall purpose of this chapter is two-fold. First, cognitive resilience to frailty will be characterized across three age-sensitive domains of cognition, namely memory, speed, and EF. Second, differences in predictors of frailty-resilient cognitive trajectories will be examined, and predictors of resilience will be compared across the included cognitive domains. More specifically, utilizing the same longitudinal dataset as in Chapter Two, these aims will be achieved through three Research Goals (RGs).

Research Goals and Proposed Procedures: Research Goal One (RG1) will examine frailty trajectory classification using the entire sample. Specifically, Latent Class Growth Analysis (LCGA) will be used to classify participants into frailty trajectory classes based on level and slope of individualized frailty trajectories (Hayden et al., 2011; Jung & Wickrama, 2008; Nylund, Asparouhov, & Muthen, 2007; Pietrzak et al., 2015; Thibeau et al., 2019). While one to three-class models will be tested (Grimm, Ram, & Estabrook, 2016), it is expected that a two-class model will be the best fit for the data. The expected two-class model will identify two

frailty trajectory classes: one with higher (worse) frailty, characterized by higher frailty level and a steeper increase in frailty, and another with lower (better) frailty, characterized by lower frailty level and more gradual increase in frailty or a relatively stable frailty trajectory (no frailty change).

Research Goal Two (RG2) will examine cognitive resilience trajectory classification using the class of higher (worse) frailty established in RG1, separately for all three cognitive domains, using LCGA. Similarly, to McDermott and colleagues (2017), two subclasses must be identified using LCGA. A subclass of resilient individuals will be characterized by higher cognitive performance and stable cognitive trajectories, and a subclass of non-resilient individuals will be characterized by lower cognitive performance and steeper cognitive decline. For example, LCGA will be used to test one-three class memory models and assess model fit using only the individuals classified as having higher (worse) frailty. This procedure will be repeated for speed, and EF. It is expected that a two-class model will fit the data best for each of the cognitive domains, classifying resilient individuals with relatively higher cognitive performance and little cognitive change from non-resilient individuals with relatively lower cognitive performance and steeper decline over time.

Research Goal Three (RG3) will establish predictors of cognitive resilience and non-resilience to frailty. For RG3, Random Forest Analyses (RFA) will be used to identify salient predictors of cognitive resilience and non-resilience from genetic, lifestyle, and demographic domains. Specifically, the thirteen predictors tested will be age, education, sex, marital status, living status, pet ownership, *APOE* and *BDNF* risk status, social activity, cognitive activity, volunteer activity, smoking, and alcohol use. These thirteen predictors are not included in the comprehensive 50-item frailty index, and so are able to be included as predictors of cognitive

resilience to frailty. It is expected that predictors such as education, age, cognitive activity, and sex will discriminate between resilient and non-resilient groups.

Finally, the last step in this proposed research is the interpretation of the results. Specifically, the predictor profiles of resilient and non-resilient individuals will be compared across cognitive domains. It is expected that age, sex, *APOE* non-risk, and education will be robust predictors of resilience across all three cognitive domains, but that other predictors of resilience will differ based on cognitive domains. For example, *BDNF* may be predictive of EF resilience to frailty but not memory resilience, based on previous associations with EF (Thibeau et al., 2016).

Significance. This chapter will provide two novel contributions. First, it will define and establish cognitive resilience in the light of frailty. Second, it will identify set of factors which contribute to the development or maintenance of resilience in aging and compare these predictive factors across all three domains of cognitive function. This research contributes to the field of cognitive aging in several ways. Resilience is a multidimensional phenomenon, arising from the combination or interaction of several protective resources and risk factors. First, this chapter aims to quantify the discordance between frailty and high cognitive function, by characterizing and defining cognitive resilience to frailty. Second, this chapter aims to identify factors which foster cognitive resilience to frailty. Identifying and understanding underlying predictors of cognitive resilience in the face of physical health adversity may allow future research a basis for comparison and examination of cognitive resilience to other types of adversity. As there is now established empirical evidence behind risk factors for dementia (Dixon & Lachman, 2019; Livingston et al., 2017), it is conceivable that this research may add to the establishment of similar evidence for factors that promote cognitive resilience. Third, increasing cognitive

resilience, considering the multi-dimensional health challenges faced by older adults, offers an opportunity for multifactorial intervention and assistance for this particularly vulnerable population.

Chapter Three. Building on the framework provided by the previous chapters, Chapter Four will be entitled "Cognitive Resilience: The Crossroads of Low Mobility and High Cognitive Performance". The overall purpose of this chapter is to establish whether individuals can maintain cognitive function despite low and declining mobility (gait, balance) performance. Additionally, it will examine differences in salient predictors of cognitive resilience to low mobility, identifying factors that differentiate resilient from non-resilient participants. Using the same longitudinal dataset as used in the previous two chapters, three RGs will allow systematic investigation of cognitive resilience to low mobility.

Research Goals and Proposed Procedures. In this chapter, mobility (gait and balance) will be measured by two VLS tasks, timed walk and timed turn. Gait is measured as a timed walk (in s) over a distance of 20 feet. Balance is measured as timed turn (in s), i.e., how fast a person could make a complete circle from a standing position. A composite mobility score was formed with unit weighted z-scores of the two indicators, in which higher scores will indicate better mobility performance (Buchman et al., 2007; Swank, Almutairi, & Medley, 2017). Foundational analyses will establish a mobility growth model and examine mobility trajectory classification. Specifically, latent growth modeling will be used to test variability in intra-individual patterns of change over time for mobility. Growth models will be tested in this order: (a) a fixed intercept model, which assumed no inter- or intra-individual variation, (b) a random intercept model, which modeled inter-individual variability in overall level but no intra-individual change, (c) a random intercept fixed slope model, which allowed inter-individual variability in level but

assumes all individuals exhibited the same rate of change, and (d) a random intercept, random slope model which allowed inter-individual variability in level and change. Second,

Research Goal One (RG1) will examine mobility trajectory classification. Specifically, LCGA will be used to classify participants into mobility trajectory classes based on level and slope of the mobility growth model established in the foundational analyses. While one- to three-class models will be tested, it is expected that two classes of mobility will provide the best fitting model. The expected two-class model will distinguish a higher (better) performing mobility class and a lower (worse) performing mobility class. It is expected that the higher mobility class will be characterized by relatively higher mobility performance and relatively stable trajectories over time, and the lower mobility class will be characterized by relatively lower level of mobility and steeper decline over time.

Research Goal Two (RG2) will examine cognitive resilience trajectory classification using the lower mobility subclass established in RG1, separately for all three cognitive domains. Specifically, using a similar procedure to Chapter Three, LCGA will be applied to trajectory data for each cognitive measure within the lower mobility subclass to identify resilient and non-resilient subclasses. The resilient subclass will be comprised of individuals with lower overall mobility and higher cognitive performance (are in the higher performing classes for each of the cognitive domains). The non-resilient subclass will be comprised of those who are in the lower mobility class and have lower cognitive performance. This resilience and non-resilience classification will be performed for all three cognitive domains. For each domain, one- to three-class models will be tested, but it is expected that a two-class model will provide the best fit for the data.

Research Goal Three (RG3) will establish predictors of cognitive resilience and non-resilience to lower mobility. For RG3, Random Forest Analyses (RFA) will be used to identify salient risk and biomarker predictors that differentiate between resilient and non-resilient subclasses. As in Chapter Three, the core set of 13 predictors will be tested. These core 13 predictors are age, education, sex, marital status, living status, pet ownership, *APOE*, *BDNF* genetic risk status, social activity, cognitive activity, volunteer activity, alcohol use, and smoking. Additionally, an additional nine factors will be tested. Specifically, these additional predictors are physical activity, BMI, PP, peak expiratory flow, grip strength, diabetes, depressive symptoms, subjective health, and anti-inflammatory medication. It is expected that several factors will predict memory resilience to low mobility: younger age, *APOE* non-risk genetic status, *BDNF* non-risk status, female sex, high education, and high cognitive activity.

Finally, the last step in this research is the interpretation of the results. Similar to Chapter Three, the biomarker predictors of resilient and non-resilient classes will be compared and contrasted for generalizability across cognitive domains for mobility. It is expected that several predictors of resilience to lower mobility will be robust across all three cognitive domains.

Significance. This chapter will offer the opportunity to identify predictors of resilience despite another commonly occurring physical deficit for older adults (lower mobility). Identifying predictors of cognitive resilience and comparing them across multiple types of adversities associated with cognitive decline allows for the possible identification of a core set of common factors. This is conceptually similar to research over the past decade that has identified modifiable risk factors that contribute to dementia (Livingston et al., 2017) and therefore allowed for generalized recommendations to be made to reduce dementia risk. If we are able to establish a core set of common factors that foster resilience, we may identify opportunities for older adults

to enhance their cognitive performance and maintain their cognition over a long period of time. If not, we will identify resilience predictors that are specific to different cognitive domains.

Summary of Three Chapters: The three chapters included in this dissertation are united by their responsiveness to the global issue of population aging. With the expansion of the aging population, and with the expected continuing rise in dementia prevalence, research on risk and protective factors for brain and cognitive aging is imperative. The present chapters investigate the theme of resilience across three domains of cognitive change in the context of two compelling sources of exacerbated cognitive decline (frailty, mobility deficits). They are framed by a developmental lifespan perspective, taking a longitudinal approach to examining dementia prevention from the salutogenic orientation of cognitive resilience. Utilizing a core dataset comprised of non-demented older adults and modern statistical procedures, cognitive resilience is defined and established relative to two major predictors of cognitive decline, impairment, and dementia. These three chapters are programmatic in that they take a systematic, step-by-step approach to developing an understanding of the dynamics and predictors of cognitive resilience across three key age-sensitive cognitive domains. They differ in that Chapter Two establishes the cognitive influence of a major AD risk factor, while Chapters Three and Four establish the emerging complex construct of cognitive resilience. Together, they offer a significant contribution to the emerging field of resilience in aging.

Section Four: Significance

Resilience is commonly defined as the ability to avoid negative outcomes despite the presence of significant risk factors (Staudinger & Greve, 2016) and adversity (Anstey & Dixon, in press). It is related to, but different from, concepts such as cognitively successful or exceptional aging, including super brain aging (Dixon & Lachman, 2019). The concept of

resilience has specific application to AD risk-reduction; cognitive resilience is the ability to maintain relatively high levels of cognitive performance despite harboring a major adversity associated with cognitive decline, impairment, or dementia. Whilst an important psychological phenomenon, the concept of cognitive resilience also provides considerable benefit for older adults. Identifying and stabilizing, or even increasing conditions that are protective to cognitive functioning has enormous potential for delaying the onset of dementia. This in turn may have substantial economic and psychosocial impact for society, families, caregivers, and individuals.

Notably, emerging empirical evidence on cognitive resilience has the potential to provide the foundation for proposing dementia prevention interventions. Although a relatively new field of research, current literature in this area has already identified a couple of common factors of cognitive resilience to AD risk, including high education and cognitive activity (Kaup et al., 2015; McDermott et al., 2017). However, it is important to note the developmental phenomena of cognitive resilience may result from various unique combinations or constellations of risk/protective factors (Staudinger & Greve, 2016). Therefore, resilience profiles or constellations may have common components which could be generalizable to older adults and be comprised of specific factors unique to the individual. As such, deep examination of cognitive resilience across a variety of adversities may inform both generalized and precision interventions targeted to build resilience in subpopulations of older adults with high risk for AD. Precision medicine is an emerging approach which takes into account each individual's genetic, environmental, lifestyle, and psychosocial characteristics (Reitz, 2016). Precision medicine aims to make disease prevention more effective by understanding the likelihood of an individual to respond to a specific therapeutic approach (Reitz, 2016). Therefore, when this approach is applied to the area of cognitive resilience, individuals with differing AD risk factors may all be

advised to increase cognitive activity yet have other precision recommendations unique to their presenting risk constellation. While these types of interventions remain to be developed and examined, this dissertation research identifies key factors that influence AD resilience, furthering our understanding of this important phenomenon. In addition to conceptualizing, defining, and supplementing the emerging research on cognitive resilience, this dissertation may provide future opportunities for older adults to intervene in their cognitive development, adapting effective strategies for building their capacity to offset decline and impairment.

Table 1-1

Comparison of Predictors Used in Recent Resilience Studies

Cognitive Activity*	Kaup et al., 2015	Thibeau Dissertation
Demographic		
Age*	Age*	Age
Education*	Education*	Education
Marital Status*	Marital Status	Marital Status
Living Status*	Living Status	Living Status
Pet Ownership*		Pet Ownership
	Sex*	Sex
	Higher Financial Status	
	Literacy Level*	
Functional/Health		
PP*		PP
PEF*		PEF
Grip Strength		Grip Strength
BMI	Obesity (BMI over 30)	BMI
	Hypertension	
Subjective Health*		Subjective Health
Depressive Symptoms*	Depression	Depressive Symptoms
Diabetes	Diabetes*	Diabetes
Anti-inflammatory Meds*		Anti-inflammatory Meds
Statin Use		
Head Injury		
	Sleep Time	
	Myocardial Infarction	
	High Cholesterol	
	Stroke	
	High Inflammation Level	
	No Negative Life Events (past year)*	
Mobility		
Timed Turn*		
Timed Walk*		
Lifestyle		
Alcohol Use*	Alcohol Use	Alcohol Use
Physical Activity	Physical Activity	Physical Activity
Cognitive Activity*		Cognitive Activity
Social Visits*	Visits Family or Friends	Social Activity
Volunteer Frequency*	Volunteer Activity	Volunteer Avtivity
Smoking (excluded in final)	Smoking	Smoking (excluded in final)
	Time Spent Reading*	
Genetic		
		APOE
		BDNF

Note. PP = pulse pressure; PEF = peak expiratory flow; BMI = body mass index; *APOE* = Apolipoprotein E; *BDNF* = Brain Derived Neurotrophic Factor.

* indicates significant predictors of resilience (Kaup et al., 2015; McDermott et al., 2017)

Table 1-2
List of Predictors of Resilience Used in the Present Dissertation

Domain	Predictor	Core or Additional
Demographic	Age	Core
	Sex	Core
	Education	Core
	Marital Status	Core
	Living Status	Core
	Pet Ownership	Core
Genetic	*APOE*	Core
	BDNF	Core
Lifestyle	Social Activity	Core
	Cognitive Activity	Core
	Volunteer Activity	Core
	Smoking	Core
	Alcohol Use	Core
	Physical Activity	Additional
Functional Health	Diabetes	Additional
	Grip Strength	Additional
	Peak Flow	Additional
	BMI	Additional
	Pulse Pressure	Additional
	Anti-Inflammatory Medication	Additional

	Depressive Symptoms	Additional
	Subjective Health	Additional

Note. *APOE* = Apolipoprotein E; *BDNF* = Brain Derived Neurotrophic Factor; BMI = Body Mass Index. The core predictors are included in both Chapters Three and Four, and the additional predictors are included only in Chapter Four.

Table 1-3

Comparison of Predictors in this Dissertation with McFall and Colleagues (2019)

Thibeau Dissertation	McFall et al., 2019
Age	Age
Education	Education
Marital Status	
Living Status	Living Status
Pet Ownership	
Sex	Sex
PP	PP
PEF	PEF
Grip Strength	Grip Strength
BMI	BMI
	Heart Rate
Subjective Health	Subjective Health
Depressive Symptoms	Depressive Symptoms
Diabetes	
Anti-inflammatory Meds	
	Timed Turn
	Timed Walk
Alcohol Use	
Physical Activity	Physical Activity
Cognitive Activity	Cognitive Activity
Social Activity	Social Activity
Volunteer Activity	
Smoking	
	Self-Maintenance Activity
APOE	
BDNF	

Note. PP = pulse pressure; PEF = peak expiratory flow; BMI = Body Mass Index; *APOE* = Apolipoprotein E; *BDNF* = Brain Derived Neurotrophic Factor

Chapter Two: Frailty Effects on Non-Demented Cognitive Trajectories are Moderated by Sex and Genetic Risk

Age-related frailty reflects cumulative multisystem physiological and health decline (Mitnitski et al., 2001). Frailty increases risk of adverse brain and cognitive outcomes, including differential decline and dementia (Rogers et al., 2017; Song et al., 2011). Recently, understanding frailty and its impact has become a priority in clinical and research settings (Lim, Canevelli, & Cesari, 2018). Currently, there are two main methods of frailty measurement: (a) a phenotype model and (b) an accumulation of deficits (frailty index) model. The phenotype model defines frailty as the presence of three of five criteria: unintentional weight loss, exhaustion, weakness, slow gait, and low physical activity (Fried et al., 2001). A frailty index is formed by the ratio of health deficits present in an individual to the total number of potential deficits measured (Rockwood & Mitnitski, 2007b). In the current research, we use the Frailty Index (FI) for four main reasons: (a) the FI shows greater predictive value than other frailty measures for populations in community settings (Theou et al., 2015), (b) it is considered one of the most robust frailty assessment tools (Dent et al., 2016), (c) it is unidimensional and has high constructive validity (Widagdo et al., 2016), and (d) the total FI score (more than individual health deficits) has been found to be more predictive of adverse outcomes (Rockwood & Mitnitski, 2007).

Cognitive variables are often included in frailty indices. However, frailty and cognitive impairment may be distinct concepts that co-occur or interact in a cycle of age-related decline (Robertson et al., 2013). In fact, Armstrong and colleagues (2016) examined the association between a frailty index and global cognition. Their results indicated that higher (worse) frailty was associated with worse cognition at baseline and a faster rate of cognitive decline (Armstrong

et al., 2016). Notably, longitudinal relationships between frailty indices and specific cognitive domains are few. One study by Rolfson and colleagues (2013) indicated that over a three-year period, worse frailty index scores were associated with reduced neurocognitive speed performance. We expand and contribute to this area of research by examining the longitudinal relationships between a physical frailty index and three distinct cognitive domains, namely, memory, speed, and EF. However, as both cognitive aging and the accumulation of health deficits involve many complex, heterogeneous, interacting factors and processes (Anstey, 2014; Lim et al., 2018), the relationship between frailty and cognitive decline may be further influenced by other risk factors for AD, such as sex or *APOE* genetic risk**.**

Apolipoprotein E (*APOE*) has three major isoforms (ε2, ε3, and ε4), with the ε4 increasing the risk of cognitive decline and AD in a dose-dependent fashion (Liu, Kanekiyo, Xu, & Bu, 2013). The isoforms differentially regulate systems involved in AD pathology including (a) amyloid beta aggregation and clearance, (b) neuroinflammation, (c) lipid transport, and (d) glucose metabolism (Bennet et al., 2007; Liu et al., 2013). On its own, the ε4 allele is an established risk factor for cognitive decline in normal aging, mild cognitive impairment, and AD (Liu et al., 2013; Schiepers et al., 2012). Additionally, the ε4 allele has been considered a "frailty allele" and has been included as an indicator of frailty in some frailty indexes (Mitnitski et al., 2015). An independent association between *APOE* and frailty has not been demonstrated (Rockwood, Nassar, & Mitnitski, 2008); therefore, *APOE* may operate by way of interaction or moderation when considered in relation to cognition. In fact, *APOE* has been found to exert moderating effects on the relationship between single health factors (i.e., vascular health and PP) and cognitive change with aging (McFall, Sapkota, McDermott, & Dixon, 2016; McFall, Wiebe,

et al., 2015). As such, it is possible that *APOE* may moderate the effect of frailty on cognitive performance and change.

Sex differences in frailty have garnered a great deal of attention in the literature. Results of a recent meta-analysis showed that females had higher frailty index scores than males at all ages but a lower mortality rate at any given level of frailty or age, indicating that frailty is more lethal in males than females (Gordon et al., 2017). Additionally, sex differences in level and change trajectories are evident across many cognitive domains, with females demonstrating generally higher levels of performance and greater resilience to age-related cognitive decline than men (McCarrey et al., 2016). Notably, females are disproportionately affected by AD in severity, progression, and prevalence (Mazure & Swendsen, 2016) and female carriers of the *APOE* ε4 risk allele are at a higher risk for AD than male carriers (Altmann, Tian, Henderson, & Greicius, 2014). Moreover, females with *APOE* ε4 and higher levels of beta-amyloid burden experienced faster rates of cognitive decline than their male counterparts (Buckley et al., 2018). Taken together, sex may also influence the relationship between age-related cognitive performance and decline and frailty.

Research Goals

The overall purpose of this study was to examine relationships of both level (at a statistical centering age) and slope (longitudinal change) between frailty and three cognitive domains: (a) episodic memory, (b) neurocognitive speed, and (c) EF as moderated by two non-modifiable risk factors for AD (i.e., sex and *APOE* genetic risk). We assembled a 3-wave dataset, covering a 40-year age span (53 – 95) and used structural equation modeling to investigate three Research Goals (RG). For RG1 we examined how frailty (level or change) affected level and change in the three latent cognitive variables. For RG2 we examined whether *APOE* (risk, non-

risk) moderated the level and longitudinal frailty-cognition relationships. For RG3 we examined whether sex moderated the level and longitudinal frailty-cognition relationships.

Methods

Participants

Participants were community-dwelling older adult volunteers of the VLS. The VLS is a Canadian, large-scale, long-term investigation of neurocognitive aging, impairment, and dementia as influenced by genetic, biomedical, biological, health, lifestyle, and other factors (Dixon & de Frias, 2004). Three main sequential samples (initially aged 53-95 years) are followed at about 4-year intervals (M = 4.4-year interval). All participants provided written informed consent and all data collection procedures were in full and certified compliance (annually) with Health Research Ethics Board at the University of Alberta. As the focus of this study was to examine change in cognition as moderated by a genetic variant, participants were limited to a source subsample who had provided biofluid for genotyping between 2009 and 2011 (n = 695). This source subsample consisted of current subsets of three equivalent sequential cohorts, with present data collection occurring in the 2001 – 2015 period. The VLS cohorts were from Sample 1 (waves 6, 7, and 8), Sample 2 (waves 4 and 5), and Sample 3 (waves 1, 2, and 3). The total individualized duration is up to nine years (McFall et al., 2014). The wave-to-wave retention rates by sample ranged from 77% to 90% (see Table 2-1 for attrition rates). We note that those who did not return for a third wave of data collection (n = 44) had higher levels of frailty and lower cognitive performance at the second wave of measurement than returners. The following exclusionary criteria were applied at baseline to the source sample: (a) a diagnosis of AD or dementia (n = 0), or (b) missing data at all three waves across any one of the 50 measures used to calculate frailty index (n = 40), and (c) missing data at all three waves across any one of

the four measures used to calculate the memory, speed, or EF latent variable (n = 23). The final study sample was comprised of 632 adults at baseline (M age = 70.7, range = 53.25 – 95.45; 66.7% female; see Table 2-2 for demographic information).

Measures

Frailty Index. For each participant, the Frailty Index tallied the total number of health deficits from 50 variables (see Table 2-3) which previous work suggests is sufficient for accurately predicting adverse outcomes (Ferrucci et al., 2004). The items collected included self-report data, physical examination, and formal tests with standardized scales. All frailty items were consistent with those included in previous frailty indexes (Andrew, Mitnitski, & Rockwood, 2008; Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015; Romero-Ortuno & Kenny, 2012; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008; Song, Mitnitski, & Rockwood, 2010). As cognitive performance and change were the primary outcomes, all cognitive-related measures or reports were excluded from the present frailty index.

The Frailty Index was constructed by first recoding each variable to an interval between zero and one (see Table 2-3). For variables with two possible responses, scores were either zero (deficit absent) or one (deficit present). Variables with four or five possible responses (e.g., subjective health responses included “very poor”, “poor”, “fair”, “good”, and “very good”) had scores that reflected a range between zero and one (e.g., 0.00, 0.25, 0.50, 0.75, 1.00). For all participants we calculated the frailty index as x/50, where x was the individual participant’s number of deficits (i.e., an individual with no deficits would have a frailty score of 0). In this sample, the Frailty Index means ranged from 0.13 – 0.53 at each wave (see Table 2-2), which is similar to previous studies (Armstrong, Mitnitski, Launer, White, & Rockwood, 2015).

DNA Extraction and Genotyping. As described in previous studies (McFall, Wiebe, Vergote, Anstey, et al., 2015), the VLS collects saliva according to standard biofluid collection, stabilization, and preparation procedures from DNA Genotek technology. Genetic analyses included genotype categorization based on the presence or absence of the risk allele. *APOE* genotype was divided into dichotomous categories: ε4+ (risk) consisted of ε4ε4 and ε3/ε4 allele combinations and ε4- (non-risk) consisted of ε2ε2, ε2/ε3, and ε3ε3 allele combinations. For all analyses including *APOE*, we removed the genotype which combines the risk and protective alleles (ε2ε4; $n = 30$; McFall et al., 2014). The genotypic distribution for *APOE* was in Hardy-Weinberg equilibrium, $\chi 2 = .89$.

Measures for the Cognitive Latent Variables. The memory, speed, and EF tests included in the current study have been frequently used and validated with older adults in the VLS (and other studies). Citations indicate sources for established measurement attributes, structural characteristics, and sensitivity to health and neurological factors in older adult populations. For each set of manifest indicators, we calculated a latent variable to represent the construct.

Episodic Memory**.** We calculated a robust latent variable comprised of four manifest indicators from two memory tasks (McFall, Wiebe, et al., 2015): Word recall score on list 1, and score on list 2, Rey Auditory Verbal Learning Test list B1, and list A6.

Word Recall. Two lists of 30 content diverse English words were used to test immediate recall in a rotated design. Participants were given two minutes to study each list and five minutes to write as many words as they could recall (Dixon et al., 2004).

Rey Auditory Verbal Learning Test. A list of 15 nouns was read aloud and immediately recalled; this process was repeated for five trials (A1-A5). Then a list (B1) of 15 unrelated nouns

was read aloud and immediately recalled, measuring free recall. Then the participant was asked to recall the first list of nouns (A6), measuring recall after interference (Lezak, 1983).

Speed. We calculated a robust speed latent variable comprised of four manifest indicators from four speed tasks following established procedures (McFall et al., 2015). The tasks weresimple reaction time, choice reaction time, lexical decision, and sentence verification. Because each of the speed measures varied in complexity, we applied validated correction procedures with specific lower and upper limits as follows: (a) simple reaction time, 150 ms; (b) choice reaction time, 150 ms and 4000 ms; (b) lexical decision, 400 ms and 10000 ms; (c) sentence verification, 1000 ms and 20000 ms. Subsequent trials 3 standard deviations above the mean were removed.

Simple Reaction Time. Participants were presented with a warning stimulus (***) followed by a signal stimulus (+) in the middle of the computer screen and asked to press a key as quickly as possible when the signal stimulus appeared. Fifty trials were administered, and the latency of the 50 trials was used for analysis (Dixon et al., 2007).

Choice Reaction Time. A grid of (+) was presented on the computer screen, after a 1000 ms delay one of the (+) was changed to a square, and participants were asked to indicate the location of the square using a matching arrangement of keys on the response console. The dependent measure was the average latency across 20 trials (Palmer, MacLeod, Hunt, & Davidson, 1985).

Lexical Decision. A string of five to seven letters was presented on the computer screen. Participants were asked to identify as quickly as possible whether the letters formed an English word. The average latency across 60 trials was used for analysis (Palmer et al., 1985).

Sentence Verification. A sentence was presented on the computer screen and participants were asked to identify as quickly as possible the plausibility of the sentence. The average latency across 50 trials was used for analysis (Palmer et al., 1985).

Executive Function (EF). We calculated a robust EF latent variable comprised of four manifest EF indicators (Thibeau et al., 2017): Hayling sentence completion test, Stroop test, Brixton spatial anticipation test, and Color trails test part two.

Hayling Sentence Completion. In section A, participants listened to 15 sentences read aloud with the last word missing, completing the sentence in a way that made sense and as quickly as possible. In section B, participants again listened to 15 sentences read aloud with the last word missing, completing the sentence quickly with a word that was unrelated or unconnected to the sentence. Response speed on both sections and errors within section B were used to create an overall scaled score (ranged from [impaired] to 10 [very superior]) (Burgess & Shallice, 1997).

Stroop. In part A, participants named the color of 24 dots (blue, green, red, or yellow) as quickly as possible. In part B, participants named the ink color of 24 words (e.g., "when"). In part C, participants named the ink color of color names (blue, green, red, or yellow) by ignoring the printed word and instead stating the color of the ink (e.g., if the word blue was printed in red ink, the correct answer was red). Scores were calculated from the interference index ([Part C time – Part A time]/Part A time) which reflects slowing in response to interference (Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997).

Brixton Spatial Anticipation Test. Participants deduced simple and changing patterns by predicting the movement of a blue dot among ten possible positions on a page, which followed patterns that came and went without warning. The total errors were recorded (maximum 54) and

converted to scaled scores. An overall standardized scale resulted in scores ranging from 1 (impaired) to 10 (very superior) (Burgess & Shallice, 1997).

Color Trails Test. Participants connected the numbers 1 to 25 by alternating between pink and yellow circles while disregarding the numbers in circles of the alternate color. The latency score to complete the task was used for analysis (lower scores indicated better performance) (D'Elia, Satz, Uchiyama, & White, 1996).

Statistical Analyses

Analyses pertaining to our three RGs included confirmatory factor analyses, longitudinal measurement invariance, latent growth modeling, and moderation analyses through structural equation modeling (SEM) using Mplus 7 (Muthén & Muthén, 1998). Consistent with recommended standards and other VLS research, chronological age was coded as a continuous variable and used as the metric of change for all analyses. Age was centered at age 75, the approximate mean of the 40-year span of data, and a commonly observed inflection period in non-demented cognitive aging (Dixon, Small, MacDonald, & McArdle, 2012; Small, Dixon, & McArdle, 2011). We used robust maximum likelihood estimation methods based on all available information from every variable included in the covariance matrix, to estimate any missing values (Little, 2013).

Foundational analyses. We conducted several analyses to test and confirm basic characteristics of the data. Analyses for each cognitive variable were conducted separately (i.e., confirmatory factor analysis, measurement invariance, and latent growth modeling analyses were conducted (in that order) for the EF latent variable, then for memory, and finally for speed). All model testing, model fit indices, and chi-square difference tests are reported in Tables 2-4 to 2-7.

First, confirmatory factor analysis was used to test whether four EF manifest variables fit a single-factor EF construct, and whether this single-factor EF variable fit the data for these participants. Second, longitudinal measurement invariance was tested using (a) configural invariance, which is used to determine if the same EF measures represent the latent variable at each wave of data collection, (b) metric invariance, which is used to determine that each EF latent variable was measuring the same construct, and (c) scalar invariance, which tests whether there are mean differences at the latent mean level. Model fit was determined using standard indices: (a) chi-square for which a good fit would produce a non-significant test ($p > .05$), indicating the data are not significantly different than the model estimates, (b) comparative fit index (CFI) for which $\geq .95$ was judged a good fit and between .90 and .94 was judged an adequate fit, (c) root mean square error of approximation (RMSEA), for which $\leq .05$ would be judged good and between .06 and .08 would be judged adequate, and (d) standardized root-mean-square residual (SRMR) for which good fit is judged by a value of $\leq .08$ (Kline, 2011; Little, 2013).

Third, latent growth modeling was used to test variability in intra-individual patterns of change over time for frailty, and then separately for each cognitive domain. Growth models were tested in this order: (a) a fixed intercept model, which assumed no inter- or intra-individual variation, (b) a random intercept model, which modeled inter-individual variability in overall level but no intra-individual change, (c) a random intercept fixed slope model, which allowed inter-individual variability in level but assumes all individuals exhibited the same rate of change, and (d) a random intercept, random slope model which allowed inter-individual variability in level and change. When growth modeling uses individually varying times of observation as parameters the traditional SEM model fit indices (i.e., chi-square, RMSEA, CFI, etc) are not

available. Therefore, the log-likelihood (LL) and indices of relative fit, the Akaike (AIC) and Bayesian information criteria (BIC), are provided. The LL is the measure of the magnitude of the log-likelihood function for the particular combination of parameter estimates and observed data (Singer & Willett, 2003). It contains all parameters (sample data and the unknown parameters); smaller absolute values mean a better model fit (Singer & Willett, 2003). To compare the nested growth models, the Deviance statistic was used (*D*). The deviance statistic is -2 times the sample LL and measures the discrepancy between the current model and the full model. The difference (ΔD) between the full model and the reduced model has a chi-square distribution with degrees of freedom which is the number of constraints imposed (Singer & Willett, 2003). The ΔD value was compared to a chi-square critical value with the appropriate degrees of freedom; a significant deviance statistic indicates a better model fit than the previous model. Additionally, we evaluated the resulting parameter estimates to ensure that all variances were positive (i.e., no Heywood cases) and the resulting parameter estimates were plausible (Singer & Willett, 2003). The best growth models established a functional form of change in level and slope (one growth model each for the following: frailty, memory, speed, and EF; for a total of four growth models) and were used in the analyses for RG1-RG3.

Analyses for RG1: Independent effect of frailty on, separately, memory, speed, and EF. The best fitting frailty, memory, speed, and EF growth models according to the fit indices from the foundational analyses were used. We estimated three parallel process models to see whether (a) level of frailty predicted either level or change in (separately) memory, speed, or EF, and (b) change in frailty predicted change in (separately) memory, speed, or EF (see Figure 2-5 for parallel process model diagram). First, we tested the frailty growth model in parallel process with the memory growth model to evaluate whether frailty or change in frailty exerted important

effects on level or change in memory. Path analyses were used to determine the effects (a) level of frailty (intercept) regressed on level of memory performance (intercept), (b) level of frailty (intercept) regressed on memory change (slope), and (c) change in frailty (slope) regressed on memory change (slope). These steps were repeated using the frailty growth model in parallel process with the speed growth model, and then with the EF growth model.

Analysis for RG2: Moderation of the frailty-cognition relationships by sex. A series of steps to test sex moderation was followed. First, a model which tested the effect of frailty (intercept) regressed on both level memory (intercept) and change in memory (slope), and frailty change (slope) regressed on memory change (slope) was estimated, with all the parameter estimates constrained to be equal across sex (i.e., female and male) groups. Second, the parameters were free to vary between sex groups to examine moderation. Evidence of moderation was indicated by a significant deviance test which compared the fully constrained model to the unconstrained model (Little, 2013). This indicated a model in which the effect of frailty on memory performance and change was different for males and females fit the data better than a model for which the effect of frailty on memory level and change was the same for both groups. The same series of steps was used to test sex moderation of the frailty-speed, and then the frailty-EF relationships.

Analyses for RG3: Moderation of the frailty-cognition relationships by *APOE*. We used the *APOE* groups (i.e., risk and non-risk) and applied the aforementioned analytical moderation steps to examine *APOE* moderation of the frailty-memory relationships. The same series of steps was used to test *APOE* moderation again for the frailty-speed and then the frailty-EF relationships.

Results

Foundational Analyses

In foundational analyses we separately tested and verified longitudinal invariance for the one-factor memory, speed, and EF latent variables. The frailty, EF, speed, and memory growth models were computed over a 40-year period. Results are briefly summarized below. The specific model fit indices and model comparisons are presented in Tables 2-4 to 2-7.

Confirmatory factor analysis and measurement invariance testing. Briefly, a single-factor memory model comprised of four memory mainfest indicators fit this sample of participants, and had partial scalar invariance across time (final model fit indices: RMSEA = .07; CFI = .95; SRMR = .08; $\Delta\chi^2 = 9.88$, $\Delta df = 4$, $p = .042$). A single-factor speed model comprised of four manifest indicators fit this sample of participants, and had partial scalar invariance (RMSEA = .096; CFI = .94, SRMR = .086; $\Delta\chi^2 = 94.32$, $\Delta df = 2$, $p < .001$). A single-factor EF model comprised of four manifest indicators fit the data and had partial scalar invariance (RMSEA = .04; CFI = .97, SRMR = .08; $\Delta\chi^2 = 44.7$, $\Delta df = 4$, $p < .001$; see Tables 2-4 to 2-7 for model fit and model testing comparisons). Partial scalar invariance for all measures indicates mean differences were evident at the factor level and mean level for the majority of the indicators, and we "can proceed with making comparisons of the construct's key parameters" (Little, 2011, pg. 178).

***Latent growth models*.** First, for frailty (higher score = worse) we observed that individuals varied in level of frailty at the centering age ($b = 0.423$, $p < 0.01$), exhibited significant increase in frailty scores ($M = 0.034$, $p < 0.01$), and showed variable patterns of decline *(*$b = 0.001$, $p < 0.01$; see Figure 2-1). As can be seen in Figure 2-1, (a) the full distribution of frailty index trajectories reveals variability in level and slope and (b) the group

mean trajectory curve (in bold) documents the gradual increase in frailty over the 40-year band of aging. Second, for memory we observed that individuals varied in performance at the centering age (b = 17.745, $p < 0.01$), exhibited significant decrease in memory performance (M = -0.073, $p < 0.01$), and showed variable patterns of decline (b = 0.027, $p < 0.01$; see Figure 2-2)Third, for speed we observed that individuals varied in level of speed performance at age 75 (b = 67.849, $p < 0.01$), exhibited significant decrease in performance (M = -0.100, $p < 0.01$), and showed variable patterns of decline (b = 0.139, $p < 0.01$; see Figure 2-3). Fourth, for EF, we observed that individuals varied in level of performance at the centering age (b = 0.997, $p <$ 0.01), exhibited significant decrease in EF performance (M = -0.012, p = 0.01), and showed variable patterns of decline (b = 0.003, $p < 0.01$; see Figure 2-4).

RG1: Independent effect of frailty on cognition

Frailty predicting memory. Although baseline frailty did not predict baseline level of memory performance (b = -0.435, p = 0.189) it significantly predicted rate of memory change (b = -0.039, p = 0.032). Change in frailty did not predict change in memory (b = -0.032, p = 0.946). In sum, higher (worse) frailty was associated with more rapid memory decline than was lower (better) frailty (see Figure 2-6a).

Frailty predicting speed. Frailty level significantly predicted level of speed performance (b =-1.529, p = 0.041) but did not predict rate of change (b = -0.03, p = 0.436). Notably, change in frailty significantly predicted change (slowing) in speed performance (b = -4.463, $p < 0.001$). In sum, higher (worse) frailty was associated with slower levels of speed performance (see Figure 2-6b). Additionally, a more rapid increase in frailty was associated with a more rapid decrease in speed.

Frailty predicting EF. Frailty level significantly predicted level of EF performance (b = -0.235, p = 0.019) but did not predict rate of EF change (b = -0.01, p = 0.151). In addition, change in frailty significantly predicted change in EF performance (b = -0.217, p = 0.049). In sum, higher (worse) frailty was associated with lower levels of EF performance than was lower (better) frailty (see Figure 2-6c). Additionally, a more rapid increase in frailty was associated with a more rapid decrease in EF.

RG2: Moderation of the frailty-cognition relationships by sex

We conducted six sets of moderation analyses to examine whether sex differentially moderated the previously observed frailty-memory, frailty-speed, and frailty-EF relationships.

Sex moderation of the frailty-memory relationship. Sex moderated the frailty-memory relationship (D = 102.18, Δdf = 15, p < .001). This moderation occurred for females only. For females, frailty level predicted memory performance (b = -.892, p = .014) and change in memory (b = -0.050, p = 0.013; see Figure 2-7). Specifically, for females, higher (worse) frailty was associated with lower memory performance and steeper memory decline than was lower (better) frailty. This effect was not seen for males, as frailty did not predict level or change in memory.

Sex moderation of the frailty-speed relationship. Sex moderated the frailty-speed relationship (D = 60.82, Δdf = 15, p < .001). This moderation occurred for females only; frailty change predicted change in speed (b = -3.282, p = 0.003; see Figure 2-8). Specifically, for females, worsening frailty was associated with steeper speed decline than was lower (better) frailty. This effect was not seen for males, as frailty did not predict level or change in speed.

Sex moderation of the frailty-EF relationship. Sex moderated the frailty-EF relationship (D = 62.32, Δdf = 13, p < .001). Frailty level predicted EF performance for both males (b = -.450, p = 0.029) and females (b = -.231, p = .048; see Figure 2-9). Specifically, higher (worse)

frailty was associated with steeper EF decline than was lower (better) frailty for both males and females. As this effect occurred in both sexes, we examined this moderation further. A model with constrained intercept parameters across males and females was a significantly worse fit than the unconstrained model (D = 25.7, $\Delta df = 5$, $p < .001$). This indicates the effect of frailty on EF was stronger for males than females. Specifically, males with high levels of frailty had lower EF performance than females with the same levels of frailty.

RG3: Moderation of the frailty-cognition relationships by *APOE*

We conducted six sets of moderation analyses to examine whether *APOE* differentially moderated the previously observed frailty-memory, frailty-speed, and frailty-EF relationships. Results indicated that *APOE* moderated the frailty-memory relationship ($D = 52.62$, $\Delta df = 1$, $p < 0.001$). This moderation occurred for the *APOE* risk carriers only. Overall, frailty level predicted change in memory ($b = -0.095$, $p = 0.048$; see Figure 2-10). Specifically, for *APOE* ε4+ (risk) carriers, higher (worse) frailty was associated with steeper memory decline than was lower (better) frailty. *APOE* did not moderate the frailty-speed or frailty-EF relationships.

Discussion

The overall purpose of this research was to examine the influence of frailty across three domains of cognition, as moderated by two non-modifiable factors associated with AD. Overall, examining age-related cognitive decline through the lens of the cumulative deficit model indicated that frailty is a major risk factor for both lower cognitive performance and steeper decline. Notably, our results also indicated that risk factors for AD (i.e., sex and *APOE*) exerted differential effects on the frailty-cognition relationships.

RG1: Independent effect of frailty on, separately, memory, speed, and EF

We first examined the independent effects of frailty on three domains of cognition, memory, speed, and EF. Results indicated that worse frailty was associated with steeper memory decline. For speed and EF, results were similar worse frailty was associated with lower performance, and worsening frailty was associated with steeper decline.

Although expanding, few studies to date have examined the longitudinal relationship between specific cognitive domains and the frailty index. Notably, our results are among the first that examine the relationships between frailty level, change in frailty, and cognitive performance and change. One recent study, using the frailty phenotype, examined baseline frailty as a predictor of performance and change across multiple cognitive domains (Bunce, Batterham, & Mackinnon, 2018). Their results indicated that frailty was associated with poorer speed performance, but not speed decline over time; they also found no relationship between baseline frailty and memory performance or change (Bunce et al., 2018). Our results (using the frailty index) differ in two main ways. First, our results indicated that higher frailty was associated with steeper memory decline, a result not seen by Bunce and colleagues (2018). It is possible that the use of an accumulation of deficits model could delineate predictive effects on memory not seen using the phenotypic model. Future research could examine and compare the frailty phenotype and frailty index as predictive of longitudinal memory outcomes. Second, our results examined the cognitive influence of frailty level as well as change in frailty. Specifically, our results indicated a higher frailty level was associated with worse EF and speed performance, a result consistently supported in the literature (Avila-Funes et al., 2009; Bunce et al., 2018; Rolfson et al., 2013; Wu et al., 2015). Notably however, our results also indicated that an increase in frailty over time was associated with faster EF and speed decline, while a higher frailty level was not.

Taken together, these results may indicate that in order to ascertain the influence of frailty on speed or EF change trajectories, it is necessary to examine frailty and cognition as simultaneous change processes.

Neuropathological effects of physical frailty may affect white matter in posterior and anterior brain regions (associated with EF and speed, respectively) more so than central white matter regions (associated with memory) (Kennedy & Raz, 2009), a possible explanation for the similar relationships seen between EF and speed. In fact, EF and speed deficits are both found in cognitive impairment associated with dysfunction of the frontal-subcortical circuitry (Koga et al., 2017), which provides a unifying framework for understanding the functional and cognitive changes associated with neurodegenerative disorders (Lichter & Cummings, 2001). Notably, multiple age-related complex processes contribute to the development of frailty. Therefore, it is very likely there is pathophysiologic mechanistic overlap with some of the age-related processes that contribute to cognitive decline and impairment over the course of the lifespan (Robertson et al., 2013). Indeed, chronic inflammation has been linked to cognitive decline, AD, and frailty (Heppner, Ransohoff, & Becher, 2015; Hubbard, O'Mahony, Savva, Calver, & Woodhouse, 2009; Scott et al., 2015). Inflammatory receptors located in the hippocampus and prefrontal cortex (associated with memory and EF, respectively) may be adversely affected by the state of chronic inflammation in frailty, affecting EF and memory performance (Hubbard et al., 2009; Rosano, Marsland, & Gianaros, 2011), a possible explanation for the results seen for memory and EF. Recent analyses suggest that the deficits that accumulate in a frailty index play an important role not just in dementia risk (Song et al., 2011) but also in moderating the relationship between Alzheimer's neuropathology and the clinical expression of dementia (Wallace et al.,

2019). Those analyses, controlled for sex and *APOE* ε4 status, are consistent with what we have observed here.

RG2: Moderation of the frailty-cognition relationships by sex

The second research goal was to examine sex moderation of frailty-cognition relationships. Results indicated that frailty predicted worse cognitive performance or change across all three cognitive domains for females, but only predicted EF performance level for males. This indicates that females may experience a wider cognitive deficit from higher levels of frailty than males.

Females have a higher risk for AD than males. Additionally, females have been found to have higher levels of frailty than men, but lower levels of mortality (Hubbard & Rockwood, 2011). This may be because men may have a lower threshold for deficit accumulation than females; at any level of frailty men may have changed more from their baseline status (Gordon et al., 2017). In fact, descriptive analyses indicated that overall, women in our sample had higher frailty levels; however, men at the same frailty level had steeper frailty change trajectories than women, supporting the male-female health-survival paradox, a phenomenon in which females experience higher rates of disability and poor health but longer lives than males (Gordon et al., 2017). While some recent research has examined the effect of frailty across different domains of cognition, our study is one of the first to specifically examine sex differences within these frailty-cognition associations.

Notably, men in this study did not experience a cognitive cost of frailty on memory or speed performance or change. However, our results indicated the effect of frailty on EF performance was stronger for males than females**.** A recent study of sex differences in cognition by McCarrey and colleagues (2016) indicated that in a cognitively normal sample of older adults,

males and females experienced the same rates of decline in EF. Therefore, frailty may be a discriminating factor of cognitive differences between sexes; there may be a higher cognitive cost of frailty for males that results in a more profound EF deficit, despite more widespread cognitive deficits for females. In fact, a recent study by Gallucci and colleagues (2018) examined the association between frailty and cerebral atrophy. Their results indicated an increase in frailty was associated with an increase in cortical atrophy in the frontal and temporal lobes, an effect which was more evident in males, despite a similar level in frailty between the two sexes (Gallucci, Piovesan, & Di Battista, 2018). Taken together, the effect of frailty may have a higher impact on EF performance for males due to the higher level of frontal lobe atrophy that occurs with the accumulation of deficits.

The pathophysiologic underpinnings of frailty may differ between males and females (Gordon & Hubbard, 2018; Gordon et al., 2017). Among them, inflammatory markers, hormones, and genetic influences have all been found to exhibit both differential and systemic effects on frailty (Cawthon et al., 2009; Collerton et al., 2012; Gordon & Hubbard, 2018; Hubbard et al., 2009; Mitnitski et al., 2015). Future research should examine sex differences in physiological biomarkers of frailty, as well as examine frailty-related sex differences in brain structure and accumulation of neuropathology that could explain the frailty-cognition sex differences seen in this study.

RG3: Moderation of the frailty-cognition relationships by *APOE*

Research goal three was to examine *APOE* moderation of the frailty-cognition relationships. Our results indicated that *APOE* only moderated the association between frailty and memory. Specifically, for *APOE* risk carriers, frailty predicted significant memory decline, suggesting that genetic risk may increase vulnerability to negative health states, such as

cumulative health deficits. *APOE* ε4 is recognized as a "frailty allele" (Gerdes et al., 2000). However, the literature examining the relationship between *APOE* and frailty is sparse. One study conducted by Rockwood and colleagues (2009) found no relationship between frailty and *APOE* status. Notably, the effect of *APOE* has been found to occur in interaction with health and lifestyle factors (McFall, Wiebe, Vergote, Anstey, et al., 2015). Therefore, more information may be offered when examining *APOE* interactively, rather than as an independent influence.

APOE may moderate the relationship between frailty and memory by promoting more widespread neuropathology, particularly in the deeper, medial regions associated with memory before the onset of neurodegenerative disease (Lu, Thompson, et al., 2011). Buchman and colleagues (2013) found that the accumulation of brain pathology may contribute to frailty progression in older adults. Additionally, Bailey and colleagues (2015) found that *APOE* ε4 carriers had smaller medial temporal lobe volumes, and that the volume mediated the relationship between memory performance and *APOE* genotype. *APOE* ε4 is also associated with altered levels of C-reactive protein, a systemic marker of inflammation (Yun et al., 2015) which has been found to be associated with frailty (Velissaris et al., 2017), memory performance and lower medial temporal volume (Bettcher et al., 2012), and cognitive decline in a non-demented population (Yaffe et al., 2003). Taken together, frailty biomarkers, *APOE,* and age-related memory decline may share common pathophysiological mechanisms (i.e., brain atrophy, beta-amyloid burden, inflammatory markers) (Ruan et al., 2017).

There are several strengths and limitations to this study. A first limitation is the participants of the VLS may not be representative of the broadest population of older adults, as they are initially selected to be relatively healthy, free of neurodegenerative disease and may possess several risk-reducing factors. However, they could reflect a growing proportion of older

adults in western countries. Second, only participants from the first and third VLS cohort contributed three data points to this particular study. A more complete design would have included three data points from all samples. However, this design characteristic did not affect the results, as evidenced by the invariance testing, which showed that the EF, episodic memory, and neurocognitive speed latent variables were the same across time and could be compared at each data point. Third, we did not determine directional effects of the frailty-cognition relationship, as we examined frailty as a predictor of cognitive performance and change. Future research could examine the possibility of bidirectional frailty-cognition relationships. Fourth, we were not able to examine moderation with respect to a sex × *APOE* interaction, as these models did not converge. This non-convergence could be due to a low number of *APOE ε4+* males (n = 54) which is not sufficient for the complex analyses used to jointly model performance and change of both frailty and cognition within this study (Kline, 2011). Fifth, our present analyses do not model trajectory-based subgroups for either frailty or cognition (Mitnitski, Fallah, Dean, & Rockwood, 2014). Such trajectory subgroup analyses could potentially distinguish patterns of improvement, stability, and decline that would be valuable to investigate in future research (Canevelli et al., 2017). Regarding strengths, first, we used contemporary statistical approaches to systematically analyze three complex research goals, examining (a) longitudinal frailty-cognition relationships using three parallel process growth models, and (b) the moderating influence of two major risk factors for AD (i.e., sex, *APOE*). Second, we used multiple standard episodic memory, EF, and neurocognitive speed variables, which contributed to validated, invariant, longitudinal latent variables. This is valuable as the use of latent variables adjusts for the measurement error that affects reliability of measurement when using a single measure (Little, 2013). Third, we used an accelerated longitudinal design with age as the metric of

change, allowing age to be incorporated directly into the analyses. Fourth, we used a substantial and well-characterized longitudinal sample (Wave 1 $n = 632$) tested at 3 waves across a band of 40 years of aging. Fifth, we developed a frailty index using 50 non-cognitive and non-genetic variables that previously demonstrated effectiveness in frailty indices.

In conclusion, we found that frailty in non-demented older adults affects performance and change in three age-sensitive cognitive domains. Our results are among some of the first to contribute information about moderation of the cognitive consequences of frailty in non-demented aging (Canevelli et al., 2015). Specifically, two non-modifiable AD biomarkers differentially modified these relationships. Frailty predicted worse cognitive performance or change across all three domains of cognition for females but only for EF for males. An *APOE* moderating effect was evidenced, predicting the rate of memory decline for *APOE* risk carriers only. Our results provide further evidence of the link between frailty and cognitive decline and contribute to the idea that multifactorial mechanisms contribute to cognitive decline. Disentangling the link between frailty and cognition can offer two main benefits: (a) identification of risk factors for cognitive decline and impairment, and (b) evidence-based development of new interventions that can target both frailty and cognitive decline (Robertson et al., 2013). For example, interventions that target a large array of health factors (or overall health status) with a life-course approach (Anstey, 2014) may prove to be the best way to prevent or delay cognitive decline and perhaps impairment, and dementia.

Table 2-1
Attrition Rates per Sample and Wave

		Wave 1	Wave 2		Wave 3	
			Return	Non Return	Return	Non Return
Sample One	*n*	58	49	9 (15.5%)	38	11 (22.4%)
Sample Two	*n*	179	146	33 (18.4%)	-	-
Sample Three	*n*	394	333	61 (15.4%)	300	33 (10%)

Note. Results presented as *n* (% attrition). Due to ongoing data collection, Sample two did not contribute a third data point to this study.

Table 2-2
Baseline Descriptive Statistics by APOE Genotype

APOE	ε4+ (risk)	ε4- (non-risk)
n	146	456
Age	69.82 (8.34)	71.01 (8.86)
Range	55.0 - 87.0	53.0 - 95.0
Gender (% female)	63.7	66.9
Education (years)	15.63 (3.02)	15.15 (3.0)
Range	8.0 - 24.0	5.0 - 23.0
MMSE	28.80 (1.19)	28.70 (1.24)
Range	25.00 - 30.00	24.00 - 30.00
Frailty Score	0.12 (0.07)	0.13 (0.07)
Range	.01 - .32	.01 - .42

Note. Results presented as Mean (Standard Deviation). MMSE = Mini Mental State Exam.

Table 2-3

List of Variables Used to Construct the 50-Item Frailty Index

	Frailty Measures	Coding
SR	Stroke	0 = no 0.33 = yes, not serious 0.67 = yes, moderately serious 1 = yes, very serious
	Thyroid condition	
	Arthritis (rheumatoid and/or osteo-)	
	Osteoporosis	
	Cancer	
	Asthma	
	Migraines	
	Stomach ulcer	
	Kidney or bladder trouble	
	Gastrointestinal problems (colitis/diverticulitis, gall bladder trouble, and/or liver trouble)	
	Bronchitis or emphysema	
	Diabetes	
	High blood pressure	
	Sex-related health problems (i.e., gynecological problems or prostate problems)	
	Anaemia	
	Drug and/or alcohol dependence	
	Spinal condition and/or back trouble	
	Hardening of arteries (i.e., atherosclerosis)	

	Heart trouble	
	Other conditions (up to three)	
SR	Number of medications	0 = 0-3; 0.5 = 4-7; 1 = 8+
SR	Subjective health relative to a perfect state of health	0 = very good 0.25 = good 0.50 = fair 0.75 = poor 1 = very poor
SR	Eyesight relative to age group	
SR	Hearing relative to age group	
SR	Health has affected ability to do chores	0 = no change, improved, N/A 0.25 = slightly reduced 0.50 = moderately reduced 0.75 = drastically reduced 1 = gave up doing activity
SR	Health has affected ability to get around town	
SR	Health has affected ability to do mental recreational activities	
SR	Health has affected ability to do physical recreational activities	
SR	Health has affected ability to do hobbies	
SR	Health has affected ability to socialize	
SR	Health has affected ability to travel	
SR	Stay at home but in chair most of the time	0 = no; 1 = yes
SR	Number of times sick in bed all day in the past year	0 = 0-3; 1 = 4+
SR	Number of times confined to hospital in the past year	0 = 0; 0.5 = 1-2; 3+ = 1
SR	Feeling short of breath	0 = no; 1 = yes
SR	Use of a walker, cane, or wheelchair	0 = no; 1 = yes

M	Resting heart rate (bpm)	0 = 60-99; 1 = <60 or 100+
M	Pulse pressure (mmHg)	0 = 52-63; 0.5 = 64-75.9; 1 = 76+
M	Peak expiratory flow (L/min)	Men: 0 = >340; 1 = ≤340 Women: 0 = >310; 1 = ≤310
M	Body mass index (kg/m^2)	0 = 18.5-25 0.5 = 25-<30 1= <18.5 or ≥30
M	Grip strength (kg)	Men: For BMI ≤24, GS ≤29 For BMI 24.1-28, GS ≤30 For BMI >28, GS ≤32 Women: For BMI ≤23, GS ≤17 For BMI 23.1-26, GS ≤17.3 For BMI 26.1-29, GS ≤18 For BMI >29, GS ≤21
M	Timed walk	0 = ≤10s; 1 = >10s
M	Timed turn	0 = < 90th percentile 1 = within 90th percentile
M	Finger dexterity	0 = < 90th percentile 1 = within 90th percentile

SR	CES-D “during the past week, my sleep was restless”	0 = rarely or none of the time 0.33 = some or a little of the time 0.67 = occasionally or a moderate amount of the time 1 = most or all of the time
SR	CES-D “during the past week, I felt depressed”	
SR	CES-D “during the past week, I felt lonely”	
SR	CES-D “during the past week, I could not get going”	
SR	Bradburn negative affect (restless, lonely, bored, depressed, upset due to criticism)	0 = no to all 0.2 = yes to one 0.4 = yes to two 0.6 = yes to three 0.8 = yes to four 1 = yes to all
SR	Physical activity at least 2-3 times per week	0 = yes; 1 = no

Note. SR = Self-reported; M = measured; CES-D = Center for Epidemiological Studies Depression Scale

Table 2-4

Growth Model Goodness of Fit Index for Frailty

Model	-2LL	AIC	BIC	D	Δdf	*p*
Frailty						
Fixed intercept	3538.08	3546.07	3563.87			
Random intercept	2927.16	2937.16	2959.40	610.92	1	< .001
Random intercept, fixed slope	2732.76	2744.77	2771.46	194.40	1	< .001
Random intercept, random slope*	**2695.56**	**2711.96**	**2747.55**	37.20	2	< .001

Note. -2LL = -2 Log likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; *D* = difference statistic (using -2LL); Δdf = change in degrees of freedom; -2LL = -2 Log likelihood

*Best fitting model

Table 2-5

Goodness of Fit Indices for Episodic Memory (EM) Confirmatory Analysis Models and Measurement Invariance Testing

Model	AIC	BIC	χ2	df	*p*	RMSEA	CFI	SRMR	Δχ2	Δdf
CFA for One Factor Model (EM)										
Configural Invariance	33838.01	34051.60	87.15	42	<.001	.04 (.03-.05)	0.99	0.04		
Metric Invariance	33839.61	34026.46	100.75	48	<.001	.04 (.03-.05)	0.98	0.05	13.60	6
Scalar Invariance	34046.29	34197.52	323.39	56	<.001	.09 (.08-.10)	0.92	0.01	222.64	6
Partial Scalar Invariance*[a]	**33937.52**	**34016.58**	**206.65**	**52**	**<.001**	**.07 (.07-.08)**	**0.95**	**0.08**	**9.88**	**4**

Model	AIC	BIC	-2LL	D	Δdf	*p*
Latent Growth Model (EM)						
Fixed intercept	84524.59	8476.39	8450.60			
Random intercept	6433.46	6455.70	6423.46	2027.14	1	<.001
Random intercept, fixed slope	6277.36	6304.06	6265.36	158.10	1	<.001
Random intercept, random slope*	**5939.34**	**5974.93**	**5923.34**	**342.02**	2	**<.001**

Note. CFA = Confirmatory Factor Analysis; AIC = Akaike information criterion; BIC = Bayesian information criterion; χ2 = chi-square test of model fit; df = degrees of freedom for model fit; RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; Δ χ2 = change in chi-square; Δdf = change in degrees of freedom; -2LL = -2 Log likelihood; D = difference statistic (using -2LL)

*Best Fitting Model

a RAVLT free recall and RAVLT recall after interference free to vary

Table 2-6

Goodness of Fit Indices for Neurocognitive Speed Confirmatory Analysis Models and Measurement Invariance Test

Model	AIC	BIC	χ2	df	*p*	RMSEA	CFI	SRMR	Δχ2	Δdf
CFA for One Factor Model (NS)										
Configural Invariance	49170.456	49424.04	173.117	33	<.001	.082 (.070-.094)	0.965	0.073		
Metric Invariance	49172.953	49399.85	187.614	39.00	<.001	.078 (.067-.089)	0.963	0.08	14.50	6
Scalar Invariance	49360.533	49551.84	391.194	47.00	<.001	.105 (.098-.118)	0.915	0.14	203.58	8
Partial Scalar Invariance*[a]	**49263.27**	**49481.27**	**281.931**	**41**	**<.001**	**.096 (.086-.107)**	**0.94**	**0.086**	**94.32**	**2**

Model	AIC	BIC	-2LL	D	Δdf	*p*
Latent Growth Model (NS)						
Fixed intercept	10601.46	10619.26	10593.46			
Random intercept	8833.83	8856.07	8823.82	1769.64	1	<.001
Random intercept, fixed slope	8775.89	8802.59	8763.90	59.92	1	<.001
Random intercept, random slope*	**8335.33**	**8370.52**	**8319.32**	444.58	2	**<.001**

Note. CFA = Confirmatory Factor Analysis; AIC = Akaike information criterion; BIC = Bayesian information criterion; χ^2 = chi-square test of model fit; df = degrees of freedom for model fit; RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; SRMR = Standardized Root Mean Square Residual; $\Delta \chi^2$ = change in chi-square; Δdf = change in degrees of freedom; -2LL = -2 Log likelihood; *D* = difference statistic (using -2LL)

*Best Fitting Model

[a] Simple Reaction Time, Lexical Decision, and Sentence Verification free to vary

Table 2-7

Goodness of Fit Indices for Executive Function (EF) Confirmatory Analysis Models and Measurement Invariance Testing

Model	AIC	BIC	χ2	df	*p*	RMSEA	CFI	SRMR	Δχ2	Δdf
CFA for One Factor Model (EF)										
Configural Invariance	22685.78	22912.67	37.40	39	0.543	.00 (.00-.03)	1	0.03		
Metric Invariance	22689.16	22889.36	52.79	45	0.199	.02 (.00-.03)	1	0.05	15.38	6
Scalar Invariance	22848.22	23012.83	277.85	53	<.001	.07 (.06-.08)	0.89	0.11	225.06	8
Partial Scalar Invariance*[a]	**22725.86**	**22908.27**	**97.49**	**49**	**<.001**	**.04 (.03-.05)**	**0.97**	**0.08**	**44.70**	**4**

Model	AIC	BIC	-2LL	D	Δdf	*p*
Latent Growth Model (EF)						
Fixed intercept	4147.60	4165.40	4139.60			
Random intercept	2503.96	2526.20	2493.96	1645.64	1	<.001
Random intercept, fixed slope	2404.46	2431.15	2392.46	101.50	1	<.001
Random intercept, random slope*	**1570.45**	**1606.05**	**1554.46**	838.00	2	**<.001**

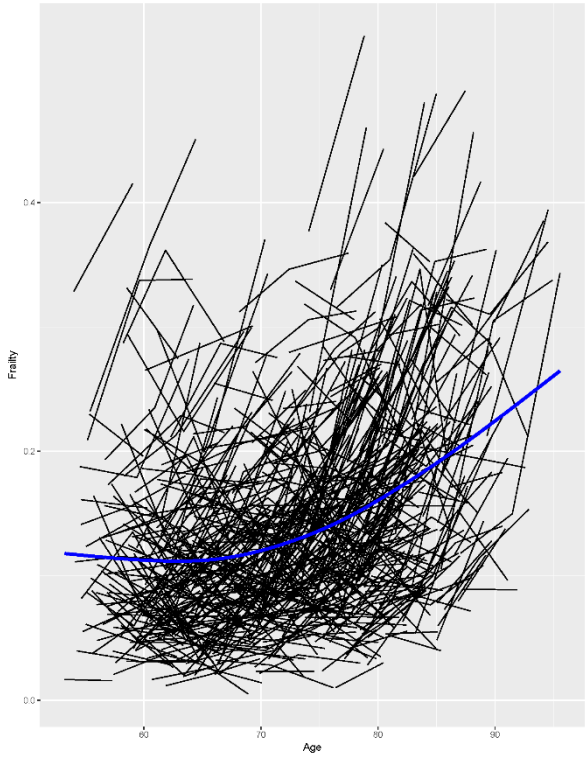
Note. CFA = Confirmatory Factor Analysis; AIC = Akaike information criterion; BIC = Bayesian information criterion; χ2 = chi-square test of model fit; df = degrees of freedom for model fit; RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; Δ χ2 = change in chi-square; Δdf = change in degrees of freedom; -2LL = -2 Log likelihood; D = difference statistic (using -2LL)

*Best Fitting Model

[a] Brixton and Color Trails free to vary

Figure 2-1

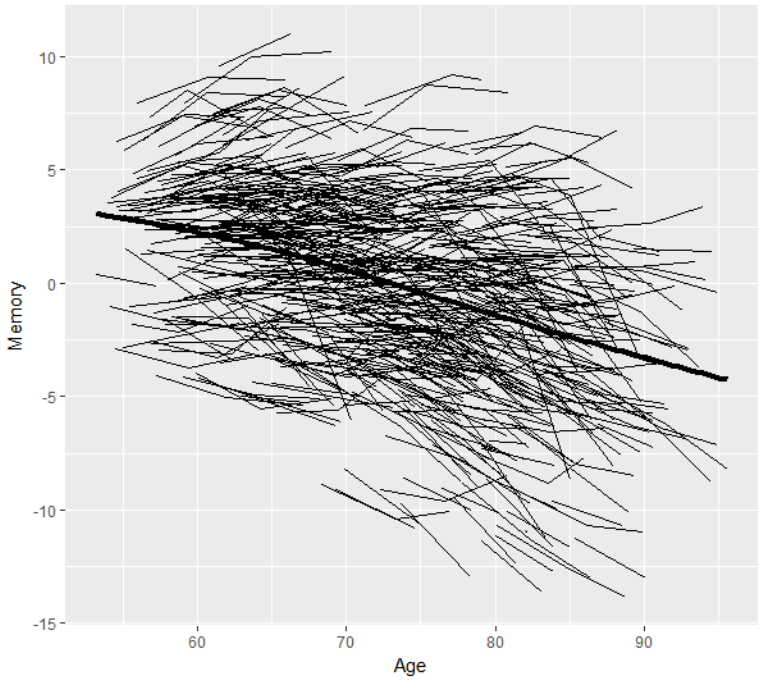
Individual Frailty Trajectories Across a 40-Year Band of Aging



Note. The blue line is the group mean trajectory (final growth model random intercept, random slope; $D = 37.2$, $\Delta df = 2$, $p < .001$).

Figure 2-2

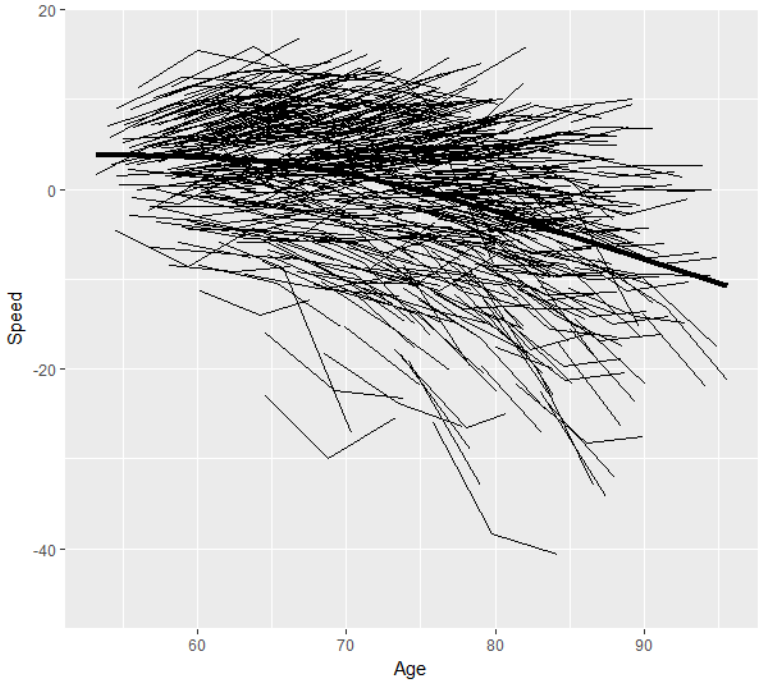
Individual Memory Trajectories Across a 40-Year Band of Aging



Note. The thick black line is the group mean trajectory line (final growth model random intercept, random slope; D = 342.02, Δdf = 2, p <.001).

Figure 2-3

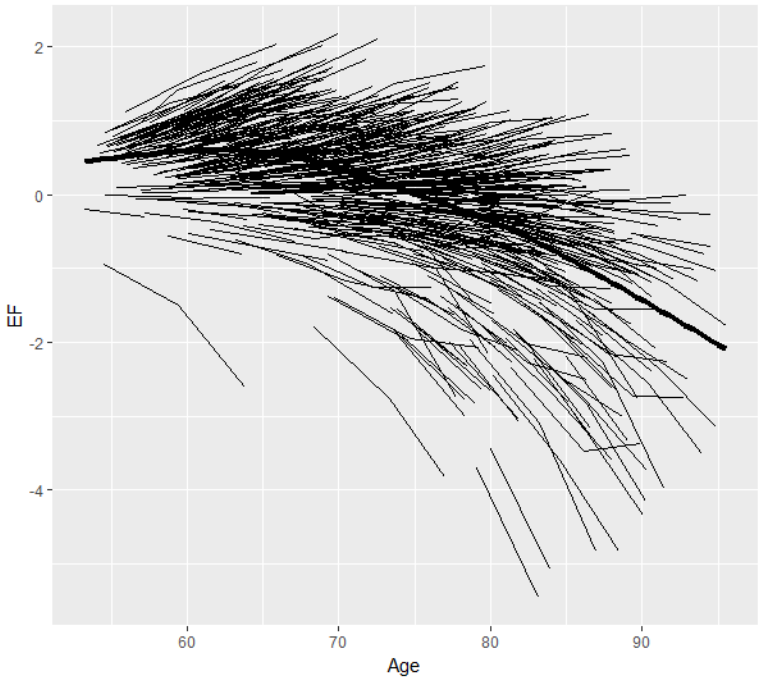
Individual Speed Trajectories Across a 40-Year Band of Aging



Note. The black line is the group mean trajectory (final growth model random intercept, random slope; D = 444.58, Δdf = 2, p <.001).

Figure 2-4

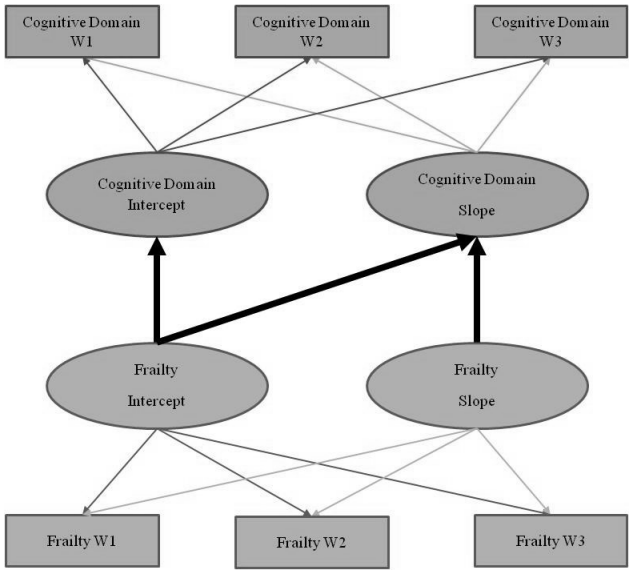
Individual Executive Function (EF) Trajectories Across a 40-Year Band of Aging



Note. The thick black line is the group mean trajectory line (final growth model random intercept, random slope; $D = 838.0$, $\Delta df = 2$, $p < .001$).

Figure 2-5

Illustration of the Frailty-Cognition Parallel Process Model

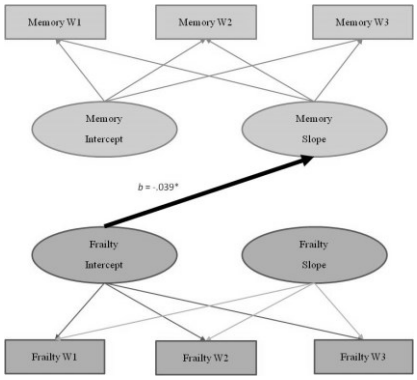


Note. The level of frailty is regressed onto level and slope of cognition, and slope of frailty is regressed onto the slope of cognition.

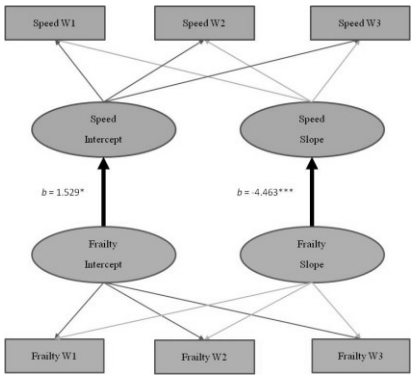
Figure 2-6

Frailty-Cognition Parallel Process Models

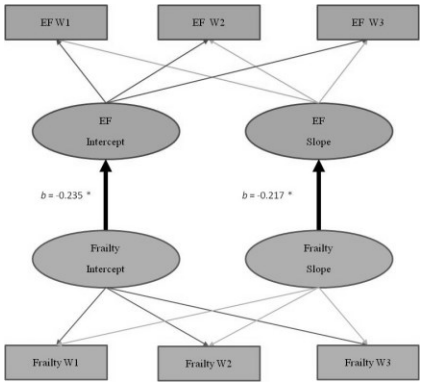
6a.



6b.



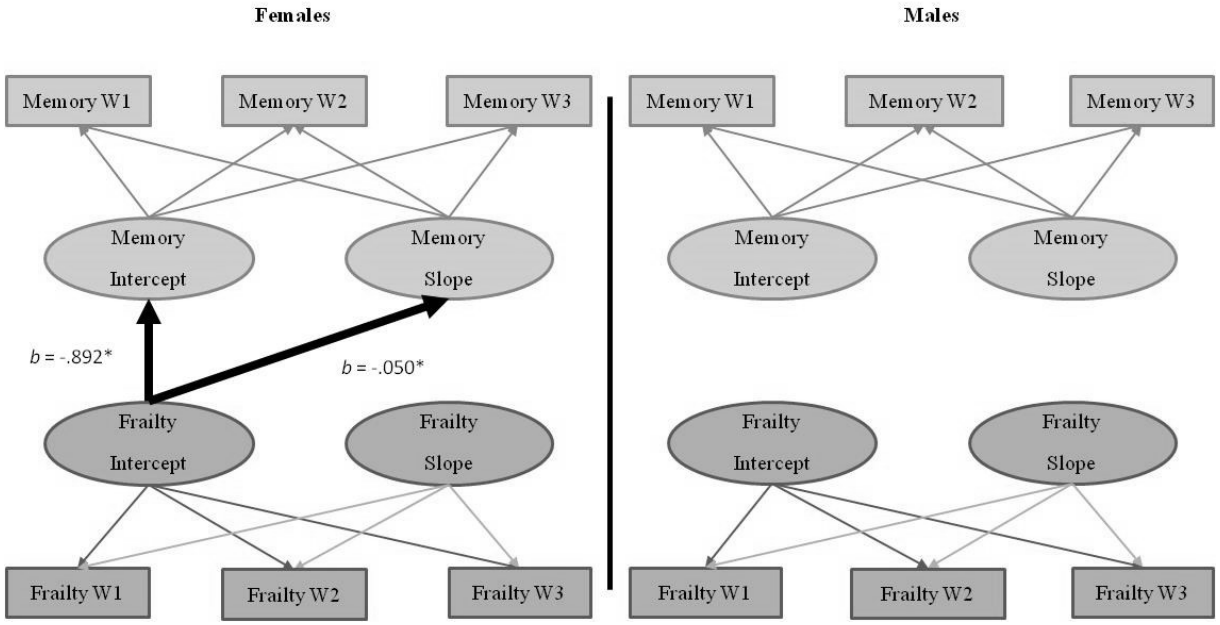
6c.



Note. Age in years was the metric of change. The age variable was centered at 75 years. Figure 6a is the frailty-memory parallel process model. Figure 6b is the frailty-speed parallel process model. Figure 6c is the frailty-executive function (EF) parallel process model. * = $p < 0.05$, *** = $p < 0.001$.

Figure 2-7

Frailty-Memory Parallel Process Model

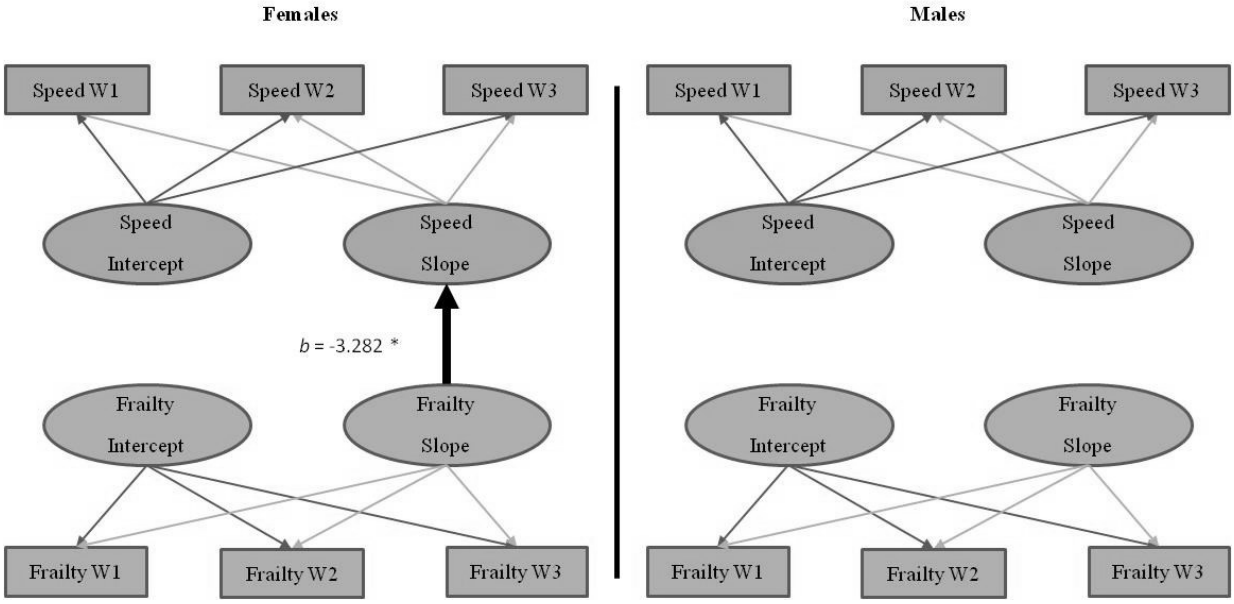


Note. This figure shows moderation by sex for change in memory. Age in years was the metric of change. The age variable was centered at 75 years.

* = $p < 0.001$

Figure 2-8

Frailty-Speed Parallel Process Model

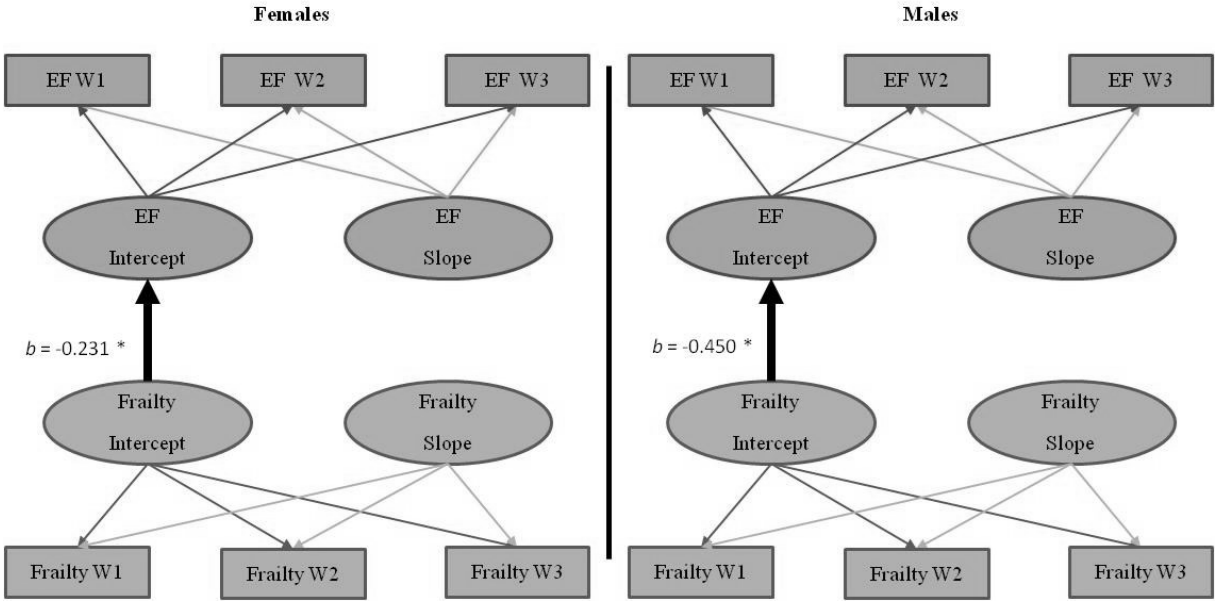


Note. This model shows moderation by sex for speed change. Age in years was the metric of change. The age variable was centered at 75 years.

* = $p < 0.05$

Figure 2-9

Frailty-EF Parallel Process Model

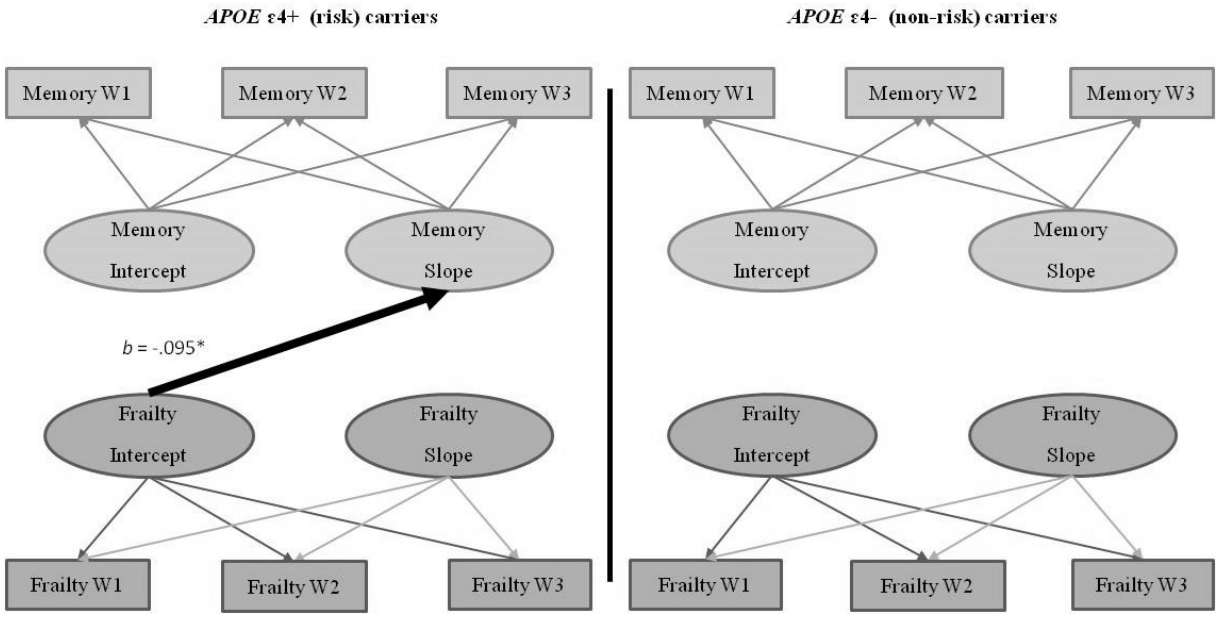


Note. This figure shows moderation by sex for change in executive function (EF). Age in years was the metric of change. The age variable was centered at 75 years.

* = $p < 0.05$

Figure 2-10

Frailty-Memory Parallel Process Model



Note. This figure shows moderation by *APOE* status. Age in years was the metric of change. The age variable was centered at 75 years.

* = $p < 0.05$

References

Altmann, A., Tian, L., Henderson, V. W., & Greicius, M. D. (2014). Sex modifies the APOE-related risk of developing Alzheimer disease. *Annals of Neurology, 75*(4), 563-573. doi:10.1002/ana.24135

Andrew, M. K., Mitnitski, A. B., & Rockwood, K. (2008). Social vulnerability, frailty and mortality in elderly people. *PLoS One, 3*(5), e2232. doi:10.1371/journal.pone.0002232

Anstey, K. J. (2014). Optimizing cognitive development over the life course and preventing cognitive decline: introducing the Cognitive Health Environment Life Course Model (CHELM). *International Journal of Behavioral Development, 38*(1), 1-10. doi:10.1177/0165025413512255

Armstrong, J. J., Godin, J., Launer, L. J., White, L. R., Mitnitski, A., Rockwood, K., & Andrew, M. K. (2016). Changes in frailty predict changes in cognition in older men: the Honolulu-Asia Aging Study. *Journal of Alzheimers Disease, 53*(3), 1003-1013. doi:10.3233/JAD-151172

Armstrong, J. J., Mitnitski, A., Launer, L. J., White, L. R., & Rockwood, K. (2015). Frailty in the Honolulu-Asia Aging Study: Deficit accumulation in a male cohort followed to 90% mortality. *Journals of Gerontology: Series A, 70*(1), 125-131. doi:10.1093/gerona/glu089

Avila-Funes, J. A., Amieva, H., Barberger-Gateau, P., Goff, M., Raoux, N., & Ritchie, K. (2009). Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: The Three-City Study. *Journal of the American Geriatric Society, 57*. doi:10.1111/j.1532-5415.2008.02136.x

Bailey, H. R., Sargent, J. Q., Flores, S., Nowotny, P., Goate, A., & Zacks, J. M. (2015). APOE ε4 genotype predicts memory for everyday activities. *Neuropsychology, Development, and Cognition: Section B, 22*(6), 639-666. doi:10.1080/13825585.2015.1020916

Bettcher, B. M., Wilheim, R., Rigby, T., Green, R., Miller, J. W., Racine, C. A., Yaffe, K., Miller, B. L., & Kramer, J. H. (2012). C-Reactive protein is related to memory and medial temporal brain volume in older adults. *Brain, Behavior, and Immunity, 26*(1), 103-108. doi:10.1016/j.bbi.2011.07.240

Blodgett, J., Theou, O., Kirkland, S., Andreou, P., & Rockwood, K. (2015). The association between sedentary behaviour, moderate-vigorous physical activity and frailty in NHANES cohorts. *Maturitas, 80*(2), 187-191. doi:10.1016/j.maturitas.2014.11.010

Buchman, A. S., Yu, L., Wilson, R. S., Schneider, J. A., & Bennett, D. A. (2013). Association of brain pathology with the progression of frailty in older adults. *Neurology, 80*. doi:10.1212/WNL.0b013e318294b462

Buckley, R. F., Mormino, E. C., Amariglio, R. E., Properzi, M. J., Rabin, J. S., Lim, Y. Y., Papp, K. V., Jacobs, H. I. L.,Burnham, S., Hanseeuw, B. J., Dore, V., Dobson, A., Masters, C. L., Waller, M., Rowe, C. C., Maruff, P., Donohue, M. C., Rentz, D. M., . . . & Sperling, R. A. (2018). Sex, amyloid, and APOE ε4 and risk of cognitive decline in preclinical Alzheimer's disease: Findings from three well-characterized cohorts. *Alzheimer's & Dementia*, *14*(9), 1193-1203. doi:https://doi.org/10.1016/j.jalz.2018.04.010

Bunce, D., Batterham, P. J., & Mackinnon, A. J. (2018). Long-term associations between physical frailty and performance in specific cognitive domains. *The Journals of Gerontology: Series B*, *74*(6), 919-926. gbx177-gbx177. doi:10.1093/geronb/gbx177

Burgess, P. W., & Shallice, T. (1997). *The Hayling and Brixton tests*. Thurston, Suffolk: Thames Valley Test Company.

Canevelli, M., Bruno, G., Remiddi, F., Vico, C., Lacorte, E., Vanacore, N., & Cesari, M. (2017). Spontaneous reversion of clinical conditions measuring the risk profile of the individual: from frailty to mild cognitive impairment. *Frontiers in Medicine, 4*, 184. doi:10.3389/fmed.2017.00184

Canevelli, M., Cesari, M., & van Kan, G. A. (2015). Frailty and cognitive decline: How do they relate? *Current Opinion in Clinical Nutrition and Metabolic Care, 18*(1), 43-50. doi:10.1097/MCO.0000000000000133

Cawthon, P. M., Ensrud, K. E., Laughlin, G. A., Cauley, J. A., Dam, T.-T. L., Barrett-Connor, E., Fink, H. A., Hoffman, A. R., Lau, E., Lane, N. E., Stefanick, M. L., Cummings, S. R., & Orwoll, E. S. (2009). Sex hormones and frailty in older men: The Osteoporotic Fractures in Men (MrOS) Study. *The Journal of Clinical Endocrinology & Metabolism, 94*(10), 3806-3815. doi:10.1210/jc.2009-0417

Collerton, J., Martin-Ruiz, C., Davies, K., Hilkens, C. M., Isaacs, J., Kolenda, C., Parker, C., Dunn, M., Catt, M., Jagger, C., von Zglinicki, T., & Kirkwood, T. B. L. (2012). Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: Cross-sectional findings from the Newcastle 85+ Study. *Mechanisms of Ageing and Development, 133*(6), 456-466. doi:10.1016/j.mad.2012.05.005

D'Elia, L. F., Satz, P., Uchiyama, C. L., & White, T. (1996). *Color Trails Test: Professional Manual*. Odessa, FL: Psychological Assessment Resources.

Dent, E., Kowal, P., & Hoogendijk, E. O. (2016). Frailty measurement in research and clinical practice: A review. *European Journal of Internal Medicine, 31*, 3-10. doi:10.1016/j.ejim.2016.03.007

Dixon, R. A., & de Frias, C. M. (2004). The Victoria Longitudinal Study: From characterizing cognitive aging to illustrating changes in memory compensation. *Aging, Neuropsychology, and Cognition, 11*(2-3), 346-376. doi:10.1080/13825580490511161

Dixon, R. A., Garrett, D. D., Lentz, T. L., MacDonald, S. W., Strauss, E., & Hultsch, D. F. (2007). Neurocognitive markers of cognitive impairment: Exploring the roles of speed and inconsistency. *Neuropsychology, 21*(3), 381-399. doi:10.1037/0894-4105.21.3.381

Dixon, R. A., Small, B. J., MacDonald, S. W. S., & McArdle, J. J. (2012). Yes, memory declines with aging—but when, how, and why? In M. Naveh-Benjamin & N. Ohta (Eds.), *Memory and Aging: Current Issues and Future Directions* (pp. 325-347). New York, NY: Psychology Press.

Dixon, R. A., Wahlin, Å., Maitland, S. B., Hultsch, D. F., Hertzog, C., & Bäckman, L. (2004). Episodic memory change in late adulthood: Generalizability across samples and performance indices. *Memory & Cognition, 32*(5), 768-778. doi:10.3758/bf03195867

Ferrucci, L., Guralnik, J. M., Studenski, S., Fried, L. P., Cutler, G. B., & Walston, J. D. (2004). Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: A consensus report. *Journal of the American Geriatrics Society, 52*(4), *625-634*. doi:10.1111/j.1532-5415.2004.52174.x

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., & Gottdiener, J. (2001). Frailty in older adults: Evidence for a phenotype. *Journals of Gerontology: Series A, 56*(3), M1456-156. doi:10.1093/gerona/56.3.M146

Gallucci, M., Piovesan, C., & Di Battista, M. E. (2018). Associations between the Frailty Index and brain atrophy: The Treviso Dementia (TREDEM) Registry. *Journal of Alzheimer's Disease*, *62*(4), 1623-1634. doi:10.3233/JAD-170938

Gerdes, L. U., Jeune, B., Ranberg, K. A., Nybo, H., & Vaupel, J. W. (2000). Estimation of apolipoprotein E genotype-specific relative mortality risks from the distribution of genotypes in centenarians and middle-aged men: Apolipoprotein E gene is a "frailty gene," not a "longevity gene". *Genetic Epidemiology, 19*(3), 202-210. doi:10.1002/1098-2272(200010)19:3<202::aid-gepi2>3.0.co;2-q

Gordon, E. H., & Hubbard, R. E. (2018). The pathophysiology of frailty: Why sex is so important. *Journal of the American Medical Directors Association, 19*(1), 4-5. doi:10.1016/j.jamda.2017.10.009

Gordon, E. H., Peel, N. M., Samanta, M., Theou, O., Howlett, S. E., & Hubbard, R. E. (2017). Sex differences in frailty: A systematic review and meta-analysis. *Experimental Gerontology, 89*(Supplement C), 30-40. doi:10.1016/j.exger.2016.12.021

Heppner, F. L., Ransohoff, R. M., & Becher, B. (2015). Immune attack: The role of inflammation in Alzheimer disease. *Nature Reviews Neuroscience, 16*, 358. doi:10.1038/nrn3880

Hubbard, R. E., O'Mahony, M. S., Savva, G. M., Calver, B. L., & Woodhouse, K. W. (2009). Inflammation and frailty measures in older people. *Journal of Cellular and Molecular Medicine, 13*(9B), 3103-3109. doi:10.1111/j.1582-4934.2009.00733.x

Hubbard, R. E., & Rockwood, K. (2011). Frailty in older women. *Maturitas, 69*(3), 203-207. doi:10.1016/j.maturitas.2011.04.006

Kennedy, K. M., & Raz, N. (2009). Aging white matter and cognition: Differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia, 47*(3), 916-927. doi:10.1016/j.neuropsychologia.2009.01.001

Kline, R. B. (2011). *Principles and practice of structural equation modeling* (Vol. 3rd). New York, NY: Guilford Press.

Koga, S., Parks, A., Uitti, R. J., van Gerpen, J. A., Cheshire, W. P., Wszolek, Z. K., & Dickson, D. W. (2017). Profile of cognitive impairment and underlying pathology in multiple system atrophy. *Movement Disorders, 32*(3), 405-413. doi:10.1002/mds.26874

Lezak, M. D. (1983). *Neuropsychological assessment*. New York, NY: Oxford University Press.

Lichter, D. G., & Cummings, J. L. (2001). *Frontal-subcortical circuits in psychiatric and neurological disorders*. New York, NY: Guilford Press.

Lim, W.-S., Canevelli, M., & Cesari, M. (2018). Editorial: Dementia, frailty and aging. *Frontiers in Medicine, 5*, 168. doi:10.3389/fmed.2018.00168

Little, T. D. (2013). *Longitudinal structural equation modeling*. New York, NY: Guilford Press.

Liu, C.-C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nature Reviews Neurology, 9*(2), 106-118.

Lu, P. H., Thompson, P. M., Leow, A., Lee, G. J., Lee, A., Yanovsky, I., Parikshak, N., Khoo, T., Wu, S., Geschwind, D., & Bartzokis, G. (2011). Apolipoprotein E genotype is associated with temporal and hippocampal atrophy rates in healthy elderly adults: A tensor-based morphometry study. *Journal of Alzheimers Disease, 23*(3), 433-442. doi:10.3233/JAD-2010-101398

Mazure, C. M., & Swendsen, J. (2016). Sex differences in Alzheimer's disease and other dementias. *The Lancet. Neurology, 15*(5), 451-452. doi:10.1016/S1474-4422(16)00067-3

McCarrey, A. C., An, Y., Kitner-Triolo, M. H., Ferrucci, L., & Resnick, S. M. (2016). Sex differences in cognitive trajectories in clinically normal older adults. *Psychology and Aging, 31*(2), 166-175. doi:10.1037/pag0000070

McFall, G. P., Sapkota, S., McDermott, K. L., & Dixon, R. A. (2016). Risk-reducing *Apolipoprotein E* and *Clusterin* genotypes ptotect against the consequences of poor vascular health on executive function performance and change in non-demented older adults. *Neurobiology of Aging*, *42*, 91-100. doi:10.1016/j.neurobiolaging.2016.02.032

McFall, G. P., Wiebe, S. A., Vergote, D., Anstey, K. J., & Dixon, R. A. (2015). Alzheimer's genetic risk intensifies neurocognitive slowing associated with diabetes in nondemented older adults. *Alzheimer's & Dementia, 1*(4), 395-402. doi:10.1016/j.dadm.2015.08.002

McFall, G. P., Wiebe, S. A., Vergote, D., Jhamandas, J., Westaway, D., & Dixon, R. A. (2014). IDE (rs6583817) polymorphism and pulse pressure are independently and interactively associated with level and change in executive function in older adults. *Psychology and Aging, 29*(2), 418-430. doi:org/10.1037/a0034656

McFall, G. P., Wiebe, S. A., Vergote, D., Westaway, D., Jhamandas, J., Bäckman, L., & Dixon, R. A. (2015). ApoE and pulse pressure interactively influence level and change in the aging of episodic memory: Protective effects among ε2 carriers. *Neuropsychology, 29*(3), 388-401. doi:10.1037/neu0000150

Mitnitski, A., Collerton, J., Martin-Ruiz, C., Jagger, C., von Zglinicki, T., Rockwood, K., & Kirkwood, T. B. L. (2015). Age-related frailty and its association with biological markers of ageing. *BMC Medicine, 13*(1), 1-9. doi:10.1186/s12916-015-0400-x

Mitnitski, A., Fallah, N., Dean, C. B., & Rockwood, K. (2014). A multi-state model for the analysis of changes in cognitive scores over a fixed time interval. *Statistical Methods in Medical Research, 23*(3), 244-256. doi:10.1177/0962280211406470

Mitnitski, A. B., Mogilner, A. J., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *Scientific World Journal, 1,* 323-336. doi:10.1100/tsw.2001.58

Muthén, L., & Muthén, B. (1998). Mplus User's Guide (7th edn). *Muthén & Muthén: Los Angeles, CA, USA, 2012*.

Palmer, J., MacLeod, C. M., Hunt, E., & Davidson, J. E. (1985). Information processing correlates of reading. *Journal of Memory and Language, 24*, 59–88. doi:10.1016/0749-596X(85)90016-6

Robertson, D. A., Savva, G. M., & Kenny, R. A. (2013). Frailty and cognitive impairment—A review of the evidence and causal mechanisms. *Ageing Research Reviews, 12*(4), 840-851. doi:http://dx.doi.org/10.1016/j.arr.2013.06.004

Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. *Journals of Gerontology: Series A, 62*(7), 722-727. doi:10.1093/gerona/62.7.722

Rockwood, K., Nassar, B., & Mitnitski, A. (2008). Apolipoprotein E-polymorphism, frailty and mortality in older adults. *Journal of Cellular and Molecular Medicine, 12*(6b), 2754-2761. doi:10.1111/j.1582-4934.2008.00270.x

Rogers, N. T., Steptoe, A., & Cadar, D. (2017). Frailty is an independent predictor of incident dementia: Evidence from the English Longitudinal Study of Ageing. *Scientific Reports, 7*(1), 15746. doi:10.1038/s41598-017-16104-y

Rolfson, D. B., Wilcock, G., Mitnitski, A., King, E., de Jager, C. A., Rockwood, K., Fallah, N., & Searle, S. D. (2013). An assessment of neurocognitive speed in relation to frailty. *Age and Ageing, 42*(2), 191-196. doi:10.1093/ageing/afs185

Romero-Ortuno, R., & Kenny, R. A. (2012). The frailty index in Europeans: Association with age and mortality. *Age and Ageing, 41*(5), 684-689. doi:10.1093/ageing/afs051

Rosano, C., Marsland, A. L., & Gianaros, P. J. (2011). Maintaining brain health by monitoring inflammatory processes: a mechanism to promote successful aging. *Aging and Disease, 3*(1), 16-33.

Ruan, Q., D'Onofrio, G., Sancarlo, D., Greco, A., Lozupone, M., Seripa, D., Panza, F., & Yu, Z. (2017). Emerging biomarkers and screening for cognitive frailty. *Aging Clinical and Experimental Research, 29*(6), 1075-1086. doi:10.1007/s40520-017-0741-8

Schiepers, O., Harris, S., Gow, A., Pattie, A., Brett, C., Starr, J., & Deary, I. (2012). APOE E4 status predicts age-related cognitive decline in the ninth decade: Longitudinal follow-up of the Lothian Birth Cohort 1921. *Molecular Psychiatry, 17*(3), 315-324. doi:10.1038/mp.2010.137

Scott, S. B., Graham-Engeland, J. E., Engeland, C. G., Smyth, J. M., Almeida, D. M., Katz, M. J., Lipton, R. B., Mogle, J. A., Munoz, E., Ram, N., & Sliwinski, M. J. (2015). The effects of stress on cognitive aging, physiology and emotion (ESCAPE) project. *BMC Psychiatry, 15*(1), 146. doi:10.1186/s12888-015-0497-7

Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2008). A standard procedure for creating a frailty index. *BMC Geriatrics, 8*. doi:10.1186/1471-2318-8-24

Singer, J. D., & Willett, J. B. (2003). *Applied longitudinal data analysis: Modeling change and event occurrence*. New York, NY: Oxford University Press; US.

Small, B. J., Dixon, R. A., & McArdle, J. J. (2011). Tracking cognition–health changes from 55 to 95 years of age. *Journals of Gerontology: Series B, 66B*(suppl_1), i153-i161. doi:10.1093/geronb/gbq093

Song, X., Mitnitski, A., & Rockwood, K. (2010). Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *Journal of the American Geriatrics Society, 58*(4), 681-687. doi:10.1111/j.1532-5415.2010.02764.x

Song, X., Mitnitski, A., & Rockwood, K. (2011). Nontraditional risk factors combine to predict Alzheimer disease and dementia. *Neurology, 77*(3), 227-234. doi:10.1212/WNL.0b013e318225c6bc

Taylor, S. F., Kornblum, S., Lauber, E. J., Minoshima, S., & Koeppe, R. A. (1997). Isolation of specific interference processing in the Stroop task: PET activation studies. *NeuroImage, 6*(2), 81-92. doi:10.1006/nimg.1997.0285

Theou, O., Cann, L., Blodgett, J., Wallace, L. M. K., Brothers, T. D., & Rockwood, K. (2015). Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the Survey of Health, Ageing, and Retirement in Europe. *Ageing Research Reviews, 21*, 78-94. doi:10.1016/j.arr.2015.04.001

Thibeau, S., McFall, G. P., Wiebe, S. A., Camicioli, R., & Dixon, R. A. (2017). Alzheimer's disease biomarkers interactively influence physical activity, mobility, and cognition associations in a non-demented population. *Journal of Alzheimers Disease, 60*(1), 69-86. doi:10.3233/JAD-170130.

Velissaris, D., Pantzaris, N., Koniari, I., Koutsogiannis, N., Karamouzos, V., Kotroni, I., Skroumpelou, A., & Ellul, J. (2017). C-Reactive protein and frailty in the elderly: A

literature review. *Journal of Clinical Medicine Research, 9*(6), 461-465. doi:10.14740/jocmr2959w

Wallace, L. M. K., Theou, O., Godin, J., Andrew, M. K., Bennett, D. A., & Rockwood, K. (2019). Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: A cross-sectional analysis of data from the Rush Memory and Aging Project. *The Lancet Neurology, 18*(2), 177-184. doi:10.1016/S1474-4422(18)30371-5

Widagdo, I. S., Pratt, N., Russell, M., & Roughead, E. E. (2016). Construct validity of four frailty measures in an older Australian population: A Rasch analysis. *The Journal of Frailty & Aging, 5*(2), 78-81. doi:10.14283/jfa.2016.83

Wu, Y.-H., Liu, L.-K., Chen, W.-T., Lee, W.-J., Peng, L.-N., Wang, P.-N., & Chen, L.-K. (2015). Cognitive function in individuals with physical frailty but without dementia or cognitive complaints: Results from the I-Lan Longitudinal Aging Study. *Journal of the American Medical Directors Association, 16*(10), e899-899. doi:10.1016/j.jamda.2015.07.013

Yaffe, K., Lindquist, K., Penninx, B., Simonsick, E., Pahor, M., Kritchevsky, S., Launer, L., Kuller, L., Rubin, S., & Harris, T. (2003). Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology, 61*(1), 76-80. doi:10.1212/01.wnl.0000073620.42047.d7

Yun, Y.-W., Kweon, S.-S., Choi, J.-S., Rhee, J.-A., Lee, Y.-H., Nam, H.-S., Jeong, S.-K., Park, K.-S., Ryu, S.-Y., Choi, S.-W., Kim, H. N., Cauley, J. A., & Shin, M.-H. (2015). APOE polymorphism is associated with C-reactive protein levels but not with white blood cell

count: Dong-gu Study and Namwon Study. *Journal of Korean Medical Science, 30*(7), 860-865. doi:10.3346/jkms.2015.30.7.860

Appendix A:

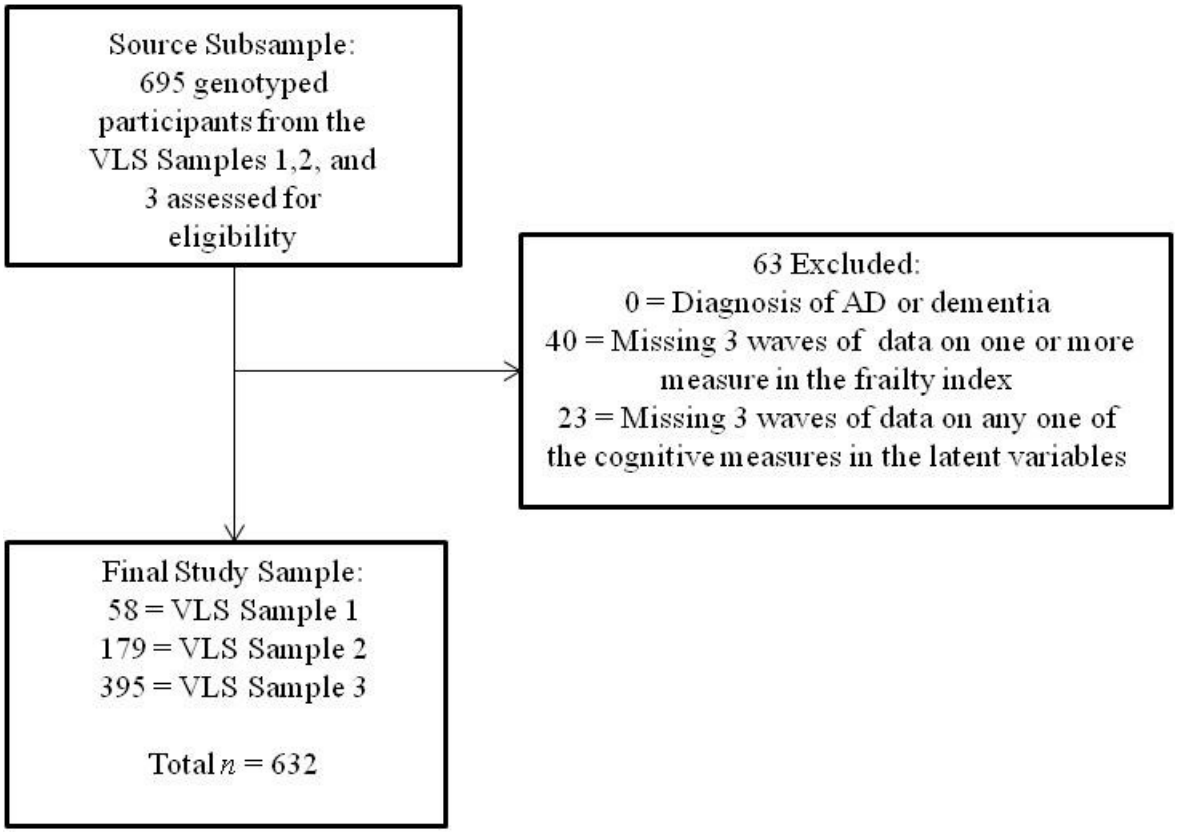
Supplementary Material for Frailty Effects on Non-Demented Cognitive Trajectories are Moderated by Sex and Alzheimer's Genetic Risk

Statistical Analyses

Parallel Process Models. We tested whether frailty predicted memory, speed, or EF using latent growth curve parallel process models. Latent growth curve parallel process models address the foundational question of whether or not there is an association between growth parameters (Little, 2013).

Figure S1

Study Flowchart of Study Participants



Note. The final sample consisted of 632 participants.

Supplementary References

Little, T. D. (2013). *Longitudinal structural equation modeling*. New York, NY: Guilford Press.

Chapter Three: Cognitive Resilience to Frailty: Definition and Determinants of Predictive Profiles

Frailty, a common condition associated with increasing age, reflects cumulative multisystem physiological and functional health decline (Mitnitski, Mogilner, & Rockwood, 2001). Frailty affects between 10 and 15% of older adults over the age of 65 and has been identified as an emerging public health priority (Cesari et al., 2016; Clegg et al., 2013). In fact, frailty has been linked to many adverse health outcomes, including a higher risk for falls, functional decline, mortality, cognitive decline, and AD (Buchman, Boyle, Wilson, Tang, & Bennett, 2007; Hoogendijk, Suanet, Dent, Deeg, & Aartsen, 2016). Our previous research found frailty was associated with cognitive performance in non-demented older adults differentially across three cognitive domains (Thibeau et al., 2019). A notable finding of this research was the empirical identification of vast heterogeneity in frailty trajectories for older adults. Specifically, non-demented older adults differed in the initial level of frailty and had highly variable patterns of frailty over time. Upon consideration, it may be possible that this overall heterogeneous distribution can be clustered into patterns representing differential patterns of frailty development and change (Caballero et al., 2020; McFall et al., 2019). Moreover, it is also possible that distinct trajectories of frailty would be differentially associated with health and cognitive outcomes. For example, it is possible that individuals with higher levels of frailty would be at a higher risk for cognitive decline, impairment, and dementia, while those with relatively stable frailty trajectories over time may be protected from cognitive decline for a longer period of time. In fact, recent research has identified differential patterns of frailty trajectories and subsequent associations with adverse health outcomes (i.e., mortality; Stow et

al., 2018). In contrast to this pathogenic approach, the present research uses a salutogenic approach to examine factors that support health and well-being despite the presence of frailty.

Resilience is a longstanding phenomenon with considerable application to cognitive aging. Resilience is defined as the ability to maintain or regain wellness despite adversity (Luthar et al., 2000). When applied to cognitive aging, resilience has been defined as the ability to preserve cognitive functioning, despite harbouring major risk factors for AD, such as age or *APOE* ε4 (Okonkwo & Vemuri, 2017; Staal, Bolton, Yaroush, & Bourne Jr, 2008). Markedly, the concept of resilience in aging brings adversity directly into the equation with the underlying assumption that everyone has a profile of risk factors detrimental to brain health (Anstey et al., 2019; Lavretsky, 2014; Livingston et al., 2017). Newly emerging research has indicated it is possible to have high genetic risk for AD, yet maintain cognitive functioning, displaying cognitive resilience (Kaup et al., 2015; McDermott, McFall, Andrews, Anstey, & Dixon, 2017). Applied to frailty, a cognitive resilience framework suggests that individuals with high levels of frailty may be able to maintain cognitive functioning.

Notably, a resilience framework also focuses on identifying other facets of health that confer resilience when risk factors for cognitive decline are present. For example, two recent studies have identified several predictors of cognitive resilience to AD genetic risk. McDermott and colleagues (2017) identified factors from demographic, lifestyle, functional biomarker, health, and mobility domains which predicted memory resilience to *APOE* and *Clusterin (CLU)* genetic risk. Kaup and colleagues (2015) identified lifestyle, psychosocial, health and demographic factors that were predictive of cognitive resilience to *APOE* genetic risk. Similar factors predicting resilience in both studies included high education and high cognitive activity. The present chapter adds to the emergent resilience research outside genetic risk, by examining

resilience considering an accumulation of health deficits. We aim to identify classes of frailty trajectories with the underlying assumption that some individuals with frailty may be cognitively resilient. Additionally, we examine a constellation of thirteen predictors to see whether these factors may discriminate between resilient and non-resilient individuals.

Research Goals

The overall purpose of the present chapter was three-fold. First, the distribution of longitudinal frailty trajectories was examined for differential classes in a large, non-demented, older adult group. Second, cognitive resilience to frailty was empirically characterized across three domains of cognition, namely memory, speed, and EF. Third, differences in predictors of frailty-resilient cognitive trajectories were examined and predictors of resilience were compared across the three cognitive domains. We assembled a distribution of individualized frailty trajectories covering a 40-year band of aging (53 – 95 years). We used data-driven analytics to investigate three research goals (RGs). For RG1 we used LCGA to classify frailty classes based on an algorithm of level and slope of the individualized frailty trajectories established in previous research (Thibeau et al., 2019). For RG2, we selected the frail class identified in RG1 and applied LCGA to each of three cognitive domain trajectory distributions. These analyses served to discriminate two subclasses of cognitive trajectories, with the higher subclass reflecting cognitive resilience to frailty and the lower subclass reflecting non-resilient trajectories. These analyses were conducted separately for the three cognitive domains. For RG3, RFA was used to identify salient predictors that discriminated the cognitively resilient from the non-resilient subclass. The same pool of 13 potential predictors was used in the models for each cognitive domain.

Methods

Participants

Participants were community-dwelling older adult volunteers of the VLS. The VLS is a large-scale, long-term Canadian investigation of human aging as influenced by genetic, biomedical, biological, health, lifestyle, and other factors (Dixon & de Frias, 2004). All participants provided written informed consent and all data collection procedures were in full and certified compliance (annually) with Health Research Ethics Board at the University of Alberta. Three main sequential samples (initially aged 53 – 95 years) are followed at about 4-year intervals (M = 4.4-year interval). As this chapter included genetic factors as predictors of cognitive resilience, participants were limited to a source subsample who had provided biofluid for genotyping between 2009 and 2011 (n = 695). This source subsample consisted of current subsets of three equivalent sequential cohorts, with present data collection occurring in the 2001 – 2015 period. The VLS cohorts were from Sample 1 (waves 6, 7, and 8), Sample 2 (waves 4 and 5), and Sample 3 (waves 1, 2, and 3). The total individualized duration is up to nine years, and we use an accelerated longitudinal design to cover a 40-year age band (McFall et al., 2014). The following exclusionary criteria were applied at baseline to the source sample: (a) a diagnosis of AD or dementia (n = 0), or (b) missing data at all three waves across any one of the 50 measures used to calculate frailty index (n = 40), and (c) missing data at all three waves across any one of the four measures used to calculate the memory, speed, or EF latent variable (n = 23). The final sample was comprised of 632 adults at baseline (M age = 70.7, range = 53.25 – 95.45; 66.9% female; see Table 2-2 for demographic information).

DNA Extraction and Genotyping. As previously described (McFall et al., 2014) the VLS collected saliva according to standard biofluid collection, stabilization, and preparation

procedures from DNA Genotek. Genetic analyses included genotype categorization based on the presence or absence of the risk allele. *APOE* genotype was divided into dichotomous categories: ε4+ (risk) consisted of ε4ε4 and ε3/ε4 allele combinations and ε4- (non-risk) consisted of ε2ε2, ε2/ε3, and ε3ε3 allele combinations. For all analyses including *APOE*, we removed the genotype which combines the risk and protective alleles (ε2ε4; n = 30; McFall et al., 2014). The genotypic distribution for *APOE* was in Hardy-Weinberg equilibrium, $\chi 2 = 0.89$. The *BDNF* genotype was divided into two categories, Met+ (risk) and Met- (non-risk). The genotypic distribution for *BDNF* was in Hardy-Weinberg equilibrium, $\chi 2=1.31$.

Measures

Frailty Index. For each participant, the Frailty Index tallied the total number of health deficits from 50 variables (see Table 3-2) which previous work suggests is sufficient for accurately predicting adverse outcomes (Ferrucci et al., 2004). The items collected included self-report data, physical examination, and formal tests with standardized scales. All frailty items were consistent with those included in previous frailty indexes (Andrew, Mitnitski, & Rockwood, 2008; Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015; Romero-Ortuno & Kenny, 2012; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008; Song, Mitnitski, & Rockwood, 2010). As cognitive performance and change were the primary outcomes in this chapter, all cognitive-related measures or reports were excluded from the present frailty index.

The FI was constructed by first recoding each variable to an interval between zero and one (see Table 3-2). For variables with two possible responses, scores were either zero (deficit absent) or one (deficit present). Variables with four or five possible responses (e.g., subjective health responses included “very poor”, “poor”, “fair”, “good”, and “very good”) had scores that reflected a range between zero and one (e.g., 0.00, 0.25, 0.50, 0.75, 1.00). For all participants we

calculated the FI as x/50, where x was the individual participant's number of deficits (i.e., an individual with no deficits would have a frailty score of 0). In this sample, the FI means ranged from 0.11 – 0.53 at each wave, which is similar to previous studies (Armstrong, Mitnitski, Launer, White, & Rockwood, 2015). For all model testing results, model fit indices, and chi-square differences tests see Chapter Two (Thibeau et al., 2019).

Measures for the Cognitive Latent Variables. The memory, speed, and EF tests included in the current chapter have been frequently used and validated with older adults in the VLS (and other studies). A previously established latent variable representing each set of manifest indicators for each (separately) of the cognitive domains was verified and used for subsequent analyses (see Chapter Two, Thibeau et al., 2019 and Tables 2-4 to 2-7 for the latent variable testing information and fit indices).

Episodic Memory. The robust latent memory variable was comprised of four manifest indicators from two memory tasks (McFall, Wiebe, et al., 2015): Word recall score on list 1, and score on list 2, Rey Auditory Verbal Learning Test list B1, and list A6. For all model testing results, model fit indices and chi-square differences tests see Chapter Two (Thibeau et al., 2019).

Word Recall. Two lists of 30 English words were used to test immediate recall in a rotated design. Participants were given two minutes to study each list and five minutes to write as many words as they could recall (Dixon et al., 2004). Six equivalent lists exist and were administered so that no participant saw the same list twice. A maximum score of 30 could be achieved on each of the two trials. The score on list 1 and score on list 2 were used as two of the four manifest variables for the latent memory construct.

Rey Auditory Verbal Learning Test. Participants listened to list of 15 nouns which was read aloud and then recalled orally as many as possible. This process was repeated for five trials

(A1-A5). Then a list (B1) of 15 unrelated nouns was read aloud and immediately recalled. Finally, the participant was asked to recall the first list of nouns (A6) (Lezak, 1983). This task provided the remaining two of the four manifest variables, list B1 was used as a measure of free recall, and list A6 was used to measure recall after interference.

Speed. A robust speed latent variable was calculated from four manifest speed tasks following established procedures (McFall et al., 2015). The tasks were: simple reaction time, choice reaction time, lexical decision, and sentence verification. Because each of the speed measures varied in complexity, we applied validated correction procedures with specific lower and upper limits as follows: (a) simple reaction time, 150 ms; (b) choice reaction time, 150 ms and 4000 ms; (b) lexical decision, 400 ms and 10000 ms; (c) sentence verification, 1000 ms and 20000 ms. Subsequent trials 3 standard deviations above the mean were removed. All model testing, model fit indices and chi-square differences tests are reported in Chapter Two, Thibeau et al., 2019.

Simple Reaction Time. Participants were presented with a warning stimulus (***) followed by a signal stimulus (+) in the middle of the computer screen and asked to press a key as quickly as possible when the signal stimulus appeared. Fifty trials were administered, and the latency of the 50 trials was used for analysis (Dixon et al., 2007).

Choice Reaction Time. A grid of (+) was presented on the computer screen, after a 1000 ms delay one of the (+) was changed to a square, and participants were asked to indicate the location of the square using a matching arrangement of keys on the response console. The dependent measure was the average latency across 20 trials (Palmer, MacLeod, Hunt, & Davidson, 1985).

Lexical Decision. A string of five to seven letters was presented on the computer screen. Participants were asked to identify as quickly as possible whether the letters formed an English word. The average latency across 60 trials was used for analysis (Palmer et al., 1985).

Sentence Verification. A sentence was presented on the computer screen and participants were asked to identify as quickly as possible the plausibility of the sentence. The average latency across 50 trials was used for analysis (Palmer et al., 1985).

Executive Function (EF). A robust EF latent variable was calculated from four manifest EF indicators (Thibeau et al., 2017): Hayling sentence completion test, Stroop test, Brixton spatial anticipation test, and Color trails test part two. For model testing results, model fit indices and chi-square differences tests are published (see Chapter Two, Thibeau et al., 2019).

Hayling Sentence Completion. In section A, participants listened to 15 sentences read aloud with the last word missing, completing the sentence in a way that made sense and as quickly as possible. In section B, participants again listened to 15 sentences read aloud with the last word missing, completing the sentence quickly with a word that was unrelated or unconnected to the sentence. Response speed on both sections and errors within section B were used to create an overall scaled score (ranged from 1 [impaired] to 10 [very superior]) (Bielak et al., 2006; Burgess & Shallice, 1997).

Stroop. In part A, participants named the color of 24 dots (blue, green, red, or yellow) as quickly as possible. In part B, participants named the ink color of 24 words (e.g., “when”). In part C, participants named the ink color of color names (blue, green, red, or yellow) by ignoring the printed word and instead stating the color of the ink (e.g., if the word blue was printed in red ink, the correct answer was red). Scores were calculated from the interference index ([Part C

time – Part A time]/Part A time) which reflects slowing in response to interference (Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997).

Brixton Spatial Anticipation Test. Participants deduced simple and changing patterns by predicting the movement of a blue dot among ten possible positions on a page, which followed patterns that came and went without warning. The total errors were recorded (maximum 54) and converted to scaled scores. An overall standardized scale resulted in scores ranging from 1 (impaired) to 10 (very superior) (Bielak et al., 2006; Burgess & Shallice, 1997).

Color Trails Test. Participants connected the numbers 1 to 25 by alternating between pink and yellow circles while disregarding the numbers in circles of the alternate color. The latency score to complete the task was used for analysis (lower scores indicated better performance) (D'Elia, Satz, Uchiyama, & White, 1996).

Predictors from risk domains. For the third research goal, a total of 13 predictive factors were included to discriminate resilient from non-resilient subclasses. These factors were included as baseline measurements from three risk domains: demographic, lifestyle, and genetic factors that were not included in the 50-item frailty index. Demographic factors included participants: (a) age in years, (b) marital status, (c) education (total years) (d) sex (male or female), (e) living status, and (f) pet ownership (yes or no). Lifestyle factors included: (a) everyday novel cognitive activity, (b) social activity, (c) volunteer activity, (d) alcohol use (yes or no), and (e) current smoking status (smoker or non-smoker). Genetic factors included risk or non-risk status for the following genes: (a) *APOE* and (b) *BDNF*. Bivariate correlations were examined for each of these predictors across each cognitive domain (see Table 3-3).

Statistical Analyses

Analyses pertaining to our RGs included LCGA through structural equation modeling using Mplus 7 (Muthén & Muthén, 1998) and RFA using R 3.2.3 (R Development Core Team, 2015). Missing data was estimated in the growth models in MPlus 7 using robust maximum likelihood estimation. For the prediction analysis, missing predictor data (1% overall, ranging from 1% to 2% across the predictor variables) were estimated using a random forest algorithm for non-parametric imputation with the "missForest" package in R for the RFA (Stekhoven & Bühlmann, 2012; Waljee et al., 2013). Preliminary statistical analyses were performed (i.e., confirmatory factor analysis, measurement invariance, and latent growth modeling) to establish the frailty growth model used for RG1.

Analyses for RG1: LCGA for Frailty Classes. A previously established frailty growth model (see Table 2-4 for model testing and fit indices) was used to perform LCGA on the full distribution of individual frailty trajectories to determine frailty status classification (frail or non-frail) based on an algorithm of individualized level and slope (Hayden et al., 2011; Jung & Wickrama, 2008; Nylund, Asparouhob, & Muthén, 2007; McFall et al., 2019; Pietrzak et al., 2015; Ram & Grimm, 2009). LCGA allows for data-driven, post-hoc classification of individual frailty trajectories using a latent categorical variable for class (Ram & Grimm, 2009). Three LCGA models were tested and compared: one, two, and three latent class frailty models (Grimm, Ram, & Estabrook, 2016). A fully constrained growth model with a random intercept, random slope was used for each model tested. The variance of both the intercept and slope were fixed to zero within the separate classes to determine differences (Berlin, Williams, & Parra, 2014). Model fit was determined using comparative fit indices (i.e., AIC, BIC, -2LL), entropy, proportion, and probability statistics, along with assessing a visual inspection of graphical model

fit (see Figure 3-1). The preferred model was identified based on the following considerations: (a) low comparative fit indices, (b) high entropy value, (c) classes comprising a substantial proportion of the sample (>10% in each class), and (d) theoretical expectation.

Analyses for RG2: Cognitive Resilience to Frailty. Using the frail class established in RG1, the same LCGA procedure was used on the distribution of individualized memory trajectories to determine resilience status classification (resilient to frailty or non-resilient to frailty) based on individualized level and slope trajectories. These steps were then repeated (separately) for speed and EF. For each latent cognitive variable, one-to-three class models were tested. Model fit was determined using comparative fit indices (i.e., AIC, BIC, -2LL), entropy, proportion, and probability statistics (see Figures 3-2 to 3-4). The preferred model was identified based on the following considerations: (a) low comparative fit indices, (b) high entropy value, (c) classes comprising a substantial proportion of the sample (>10% in each class), and (d) theoretical expectation.

Analyses for RG3: Predictors of Cognitive Resilience to Frailty. RFA (R Development Core Team, 2015) was used to determine the most important (of 13) predictors of cognitively resilient or non-resilient status from three domains (i.e., genetic, demographic, and lifestyle). RFA is a supervised machine learning classification algorithm, which combines the predictions of many single classification and regression trees (*ntree*), each of which is based on a random sample of participants and prediction variables (*mtry*). We selected RFA over multiple regression for several reasons: (a) RFA can test the importance of many predictors at the same time in the model (Strobl, Boulesteix, Zeileis, & Hothorn, 2007), (b) RFA allows for a relative ranking of important predictors, and (c) the model parameters can be adjusted to obtain completely unbiased predictors (e.g., to take the correlation between marital status and living status into account;

(Strobl, Hothron, & Zeileis, 2009). See Table 3-3 for bivariate correlations between predictor variables.

Using the Party Package in R 3.2.3 (R Development Core Team, 2015), our forest consisted of *ntree* = 5000, and at each potential split we evaluated a random sample of *mtry* = 3 predictors ($\sqrt{\#\ of\ predictors}$). Model strength was reported as the area under the receiver operating characteristic curve (AUC, using the C-statistic). Relative to this chapter, the AUC equals the probability that a randomly drawn score from the resilient subclass is higher than a randomly drawn score from the non-resilient subclass (Rice & Harris, 2005). A C-statistic of 0.5 is considered to be chance, between 0.51 and 0.59 a small effect size, between 0.6 and 0.7 a medium effect size, and 0.8 or greater is a large effect size (Rice & Harris, 2005). Permutation accuracy importance was used to define relative variable importance (Strobl, Malley, & Tutz, 2009) with the cforest package in the Party Package. Variables with negative, zero, or small positive values (left of the dotted line in Figures 3-5 to 3-7) are not important predictors of cognitive resilience to frailty. Variables beyond this range (right of the dotted line in Figures 3-5 to 3-7) are informative and interpreted with a ranking of relative importance (McDermott et al., 2017; Strobl, Hothron, et al., 2009).

Results

RG1: LCGA for Frailty Classes

The analysis indicated that a two-class model fit the data better than the one-class or the three-class models (AIC = -4813.15, BIC = -4777.60, -2LL = 4829.12; entropy = 0 .76; see Table 3-4 for comparative fit indices). The frail class was characterized by higher baseline levels of frailty and a steeper longitudinal increase of frailty (*n* = 95 [15%], intercept = 0.25, 95% CI

[0.20, 0.30], slope = 0.01, 95% CI [0.01, 0.008]). The non-frail class was characterized by lower baseline level of frailty and a stable slope or slightly increasing slope of frailty (*n* = 534 [85%], intercept = 0.11, 95% CI [-0.00, 0.12], slope = 0.003, 95% CI [.001, .005]; see Figure 3-1).

RG2: Cognitive Resilience to Frailty

Memory. The memory LCGA indicated that a three-class memory model provided the best comparative fit indices and had class proportions of >10% (AIC = 872.54, BIC = 899.79, -2LL = -850.54; entropy = 0.87; see Table 3-5 for comparative model fit indices). The high-memory subclass was characterized by high baseline memory performance and a stable slope or slightly decreasing longitudinal memory trajectory (*n* = 45 [47%], intercept = 1.71, 95% CI [1.40, 2.01], slope = -0.13, 95% CI [-0.09, -0.17]). The mid-performing memory subclass characterized by mid-level of memory performance and a slightly decreasing slope of memory (*n* = 35 [38%], intercept = -1.93, 95% CI [-2.29, -1.57], slope = -0.11, 95% CI [-0.16, -0.06]). The low-performing memory subclass characterized by low memory performance and a steeply decreasing slope (*n* =15 [16%], intercept = -5.55, 95% CI [-6.15, -4.95], slope = -0.19, 95% CI [-0.25, -0.13]). This result supports previous research that also found three subclasses of memory in an overall sample of older adults: (a) a stable memory class, (b) a normally aging memory class, (c) and a declining memory class (McFall et al., 2019). With this result and our research question in mind, three decision points were considered: (a) moving forward with the three-class model to compare only the resilient (the high performing) and non-resilient (lowest performing) classes, (b) combining two subclasses to characterize either the resilient or non-resilient subclass (e.g., similar to Kaup et al., 2015), or (c) choosing to move forward with the two-class model based on the theory and research questions guiding this examination of resilience. Theoretically, resilient brain aging may be related to, but unique and distinct from normal brain aging or

successful brain aging, therefore, using the middle class of a three-class model may not be representative of resilience, but instead represent a normally aging memory class. Upon consideration, Option A meant that a substantial part of the sample would not be considered (38%, *n* = 35) in the comparison analyses, and Option B would negate the use of the information the LCGA provided. Therefore, Option C was considered. The two-class model met all the previously established considerations of model choice: this model had low comparative fit indices (AIC = 912.69, BIC = 932.51, -2LL = -896.69), a very good entropy value (0.81), class proportions of over 10%, and aligned with the research goals of comparing resilient and non-resilient subclasses. Future research could examine the predictive differences between the three subclasses, with a refined aim of defining resilience in contrast or conceptualization of normal memory aging and declining memory aging (e.g., McFall et al., 2019).

The two-class model consisted of: (a) higher performing subclass characterized by higher baseline levels of memory performance and a stable or slightly declining memory slope (*n* = 58 [61%], intercept = 1.17, 95% CI [0.80, 1.53]), slope = -0.14, 95% CI [-0.19, -0.09]), and (b) a lower performing subclass characterized by lower baseline levels of memory performance and a declining memory trajectory (*n* = 37 [39%], intercept = -3.52, 95% CI [-3.85, -3.19], slope = -0.14, 95% CI [-0.18, -0.10]; see Figure 3-2).

Speed. The speed LCGA results indicated that a three-class speed model fit the data better than the one-class or the two-class models. However, the class proportion for the low-performing subclass fell below 10% of the sample, (0.06%, *n* = 6). Therefore, the two-class model was used (AIC = 1205.47, BIC = 1185.75, -2LL = 1169.74; entropy = 0.85; see Table 3-6 for model fit indices). The two-class model consisted of: (a) higher performing subclass characterized by higher baseline levels of speed performance and a stable or slightly declining

speed slope (*n* = 52 [55%], intercept = 3.56, 95% CI [2.58, 4.54], slope = -0.29, 95% CI [-0.39, -0.19]), and (b) a lower performing subclass characterized by worse speed performance and declining speed slope (*n* = 43 [45%], intercept = -6.36, 95% CI [-7.07, -5.65], slope = -0.40, 95% CI [-0.48, -0.32]; see Figure 3-3).

EF. The EF LCGA indicated that a two-class EF model fit the data better than the one-class or the three-class models (AIC = 300.92, BIC = 332.58, -2LL = -284.92; entropy = 0.91; see Table 3-7 for comparative model fit indices). The higher performing subclass was characterized by higher baseline levels of EF performance and a stable longitudinal EF trajectory (*n* = 66 [69%], intercept = 0.13, 95% CI [0.04, 0.21], slope = -0.02, 95% CI [-.03, -.008]). The lower performing subclass characterized by lower baseline levels of EF performance and a declining EF slope (*n* = 29 [31%], intercept = -1.0, 95% CI [-1.14, 0.86], slope = -0.02, 95% CI [-.04, -0.002]; see Figure 3-4).

RG3: Predictors of Cognitive Resilience to Frailty

RFA was used to test the relative importance of 12 factors discriminating resilient to frailty from non-resilient to frailty status for each of the cognitive domains. These 12 predictors came from three domains: demographic (i.e., age, education, sex, marital status, living status, pet ownership), genetic (i.e., *BDNF*, *APOE* genetic risk status), and lifestyle (i.e., cognitive activity, social activity, volunteer activity, alcohol use). Originally, current smoking status (smoker or non-smoker) was included but was excluded from the final list due to insufficient participant rates (*n* = 3).

Memory Resilience to Frailty. Five predictors distinguished the resilient subclass from the non-resilient subclass. Memory resilience to frailty was predicted (in order of relative importance) by being female, having higher education, being married, alcohol use, and higher

cognitive activity (C = 0.55; 95% CI [0.39 – 0.63], *ntree* = 5000, *mtry* =3). Figure 3-5 shows the predictors in order of importance, with the predictors to the right of the vertical line having the best permutation accuracy.

Speed Resilience to Frailty. RFA results indicated that only one predictor, high cognitive activity, distinguished speed resilience from non-resilience to frailty (C = 0.57, 95% CI [0.45 – 0.68], ntree = 5000, mtry = 3). Figure 3-6 shows the predictors in order of importance, as the predictors to the right of the line have the best permutation accuracy.

EF Resilience to Frailty. When examining EF resilience to frailty, RFA results indicated that three predictors distinguished the resilient subclass from non-resilient subclass. EF resilience to frailty was predicted (in order of relative importance) by younger age, high education, and high cognitive activity, Model classification performance (C) was 0.68, 95% CI [0.56 – 0.80], mtry = 3, ntree = 5000. Figure 3-7 shows the predictors in order of importance.

Generalizability of Predictors of Resilience Across Cognitive Domains. When examining the results for each cognitive domain, only high cognitive activity predicted resilience to frailty across all three domains of cognition. Memory resilience and EF resilience were both predicted by higher education (see Table 3-8).

Discussion

The overall aim of this chapter was to establish and define cognitive resilience to frailty and examine predictive factors of this newly emerging phenomenon. To address this aim, we examined three research goals by applying a series of data-driven analytics to longitudinal trajectory distributions. First, we identified distinct, separable classes of frailty trajectories for older adults. Second, we examined cognitive resilience to frailty across three cognitive domains

(i.e., memory, speed, and EF). Cognitive resilience was defined as a high level of cognitive performance and stability over time despite frailty. Third, we examined and compared predictor profiles of cognitively resilient and non-resilient individuals, separately across the three cognitive domains.

RG1: LCGA for Frailty Classes

First, using LCGA, we empirically differentiated longitudinal frailty trajectories into distinct, separable classes in a non-demented older adult population. These classes were discerned by an algorithm considering both level and slope information from individual trajectories. This methodology allowed us to study frailty change over a 40-year band of aging and identify differences in frailty trajectories over time. Specifically, results indicated that frailty trajectories were best classified into two distinct classes: a frail and a non-frail class. Consistent with the literature, individuals in the non-frail class had lower frailty scores, and more stable or slightly increasing frailty trajectories over time. Specifically, our non-frail class had a baseline mean FI score of 0.11. Recent studies have identified 0.12 as a cutoff for distinguishing between prefrail and low frail individuals (Clegg, Bates, & Young, 2016). In the present chapter, at subsequent waves the FI mean values were 0.13, and 0.13, thus indicating a low and stable trajectory over the longitudinal interval. This stability is reflected in the intercept and slope values in the growth model (viz., 0.11 and 0.003, respectively). In contrast, individuals in the frail class had higher frailty scores and worsening frailty trajectories. Notably, our frail class had a baseline mean FI value of 0.23, and slightly increasing mean FI over the subsequent measurement occasions (M = 0.26, and 0.28), consistent with the clinical cutoff for frailty (Dent, Kowal, & Hoogendijk, 2016; Searle et al., 2008). Moreover, our frail class (15.03%) is

representative of the overall occurrence of frailty (about 15%) in non-demented and community dwelling samples (Bandeen-Roche et al., 2015).

Previous studies have verified that frailty increases with age and the results of this analysis established there is vast variability in frailty trajectories. It is notable that this area of research is newly emerging with few publications addressing the variability in frailty trajectories. One recent example is research by Stow and colleagues (2018), which used similar methodology (i.e., a frailty index and LCGA) to identify distinct frail classes. Their results indicated the preferred model was a three-class model (i.e., stable, moderately increasing, and rapidly rising classes). The stable class consisted of a larger proportion of the study sample (76%) and had very little change in frailty over time. The moderately increasing class contained 21% of their sample and had a higher baseline and an increase in frailty over time. The rapidly rising class was comprised of 2% of their sample and showed a distinct increase in frailty over time. Notably, their population-based data consisted of health records of over 26000 older adults allowing a three-class model to provide the best fit for the data, even with a small proportion of the sample within the 'rapidly rising' frail class. Furthermore, they assessed mortality risk based on class membership and found that the 'rapidly rising' and 'moderately increasing' frail classes were associated with an increased chance of mortality. Another recent study by Chamberlain and colleagues (2016) examined the heterogeneity in frailty trajectories over time as stratified by age. Their results identified more variability in frailty for older adults between the ages of 60 – 69 than between 70 – 89 years of age (Chamberlain et al., 2016). Specifically, in the age range of 60 – 69, three subclasses of frailty trajectories were identified, but in the age strata of 70 – 79 and 80 – 89 only two subclasses of frailty were differentiated. Future research using data from the VLS could examine the heterogeneity in frailty trajectories as stratified by age and relative to

mortality risk. The present chapter enhances the emerging literature as it extracts the frail class and then focuses on subclasses representing objective operational definitions of either cognitive resilience or non-resilience to frailty.

RG2: Cognitive Resilience to Frailty

Using the frail class identified in RG1, cognitively higher and lower performing subclasses were identified within each domain of cognition, establishing resilient and non-resilient subclasses. These trajectory subclasses were differentiated by an algorithm considering level and slope trajectories for each individual (Cabellero et al, 2020; McFall et al., 2019) and performed separately across each cognitive domain. Results indicated that cognitive trajectories of a non-demented sample of older adults with frailty could be classified into two neighboring, yet differential secondary phenotypes (i.e., cognitively resilient to the effects of frailty, and non-resilient to frailty).

Notably, results indicated that the number of cognitively resilient individuals varied with each cognitive domain (i.e., Memory resilience n = 58 (61%); Speed resilience n = 52 (55%); EF resilience n = 66 (69%)). Upon further examination, 33% (n = 31) of the frail class were classified as cognitively resilient in all three cognitive domains, 38% (n = 36) were resilient in two out of three of the cognitive domains, 12% (n = 11) were resilient in one of three. Regarding non-resilient proportions, 18% (n = 17) were non-resilient across all three domains, 11% (n = 10) were non-resilient in two of three domains, and 39% (n = 37) were non-resilient in one of three domains. Considering these proportions, our findings are representative of the uniqueness of and vast heterogeneity within cognitive aging domains. Additionally, as far as we are aware, this is the first longitudinal study which examines resilience to frailty separately across three cognitive domains. Recently, McDermott and colleagues (2017) considered memory resilience to AD

genetic risk but did not include other age-sensitive cognitive domains. Kaup and colleagues (2015) determined cognitive resilience to AD genetic risk using a global cognition score (i.e., 3MS). While necessary and informative, simultaneously examining multiple discrete cognitive abilities allows a more comprehensive vantage point from which to investigate cognitive resilience. Future research could compare the use of global cognitive assessments with multiple domain-specific measures for determination of cognitive resilience within an older adult population.

RG3: Predictors of Cognitive Resilience to Frailty

For the third research goal, we conducted RFA comparing resilient and non-resilient subclasses across each cognitive domain. Results revealed that demographic and lifestyle factors distinguished between resilience and non-resilience to frailty. However, the predictors of resilience were mostly unique to each cognitive domain examined. Specifically, memory resilience was predicted by high cognitive activity, high education, marital status, alcohol use, and sex. EF resilience was predicted by high education, high cognitive activity, and younger age. Speed resilience was predicted only by high cognitive activity. In fact, high cognitive activity was the only common predictor of resilience across all three cognitive domains, which could speak to the beneficial ubiquitous influence of cognitive stimulation on the aging brain.
High cognitive activity and high education may contribute to resilience to frailty by enhancing cognitive performance, buffering against cognitive decline and offsetting the risk for cognitive decline and dementia (Anstey, 2014; Cheng, 2016; Clouston et al., 2020; Hultsch, Hertzog, Small, & Dixon, 1999; Lenehan, Summers, Saunders, Summers, & Vickers, 2015; Yates & Orrell, 2016). Moreover, cognitive activity and education both contribute to cognitive reserve, which protects against brain degeneration and neuronal injury associated with aging (Mungas et

al., 2018; Thow et al., 2018; Wilson et al., 2019). Similar to our results, McDermott and colleagues (2017) found education and high cognitive activity were predictors of memory resilience to AD genetic risk. Additionally, Kaup and colleagues (2015) found education and high literacy level predicted resilience to *APOE* genetic risk. In a recent study examining memory trajectory classification for older adults, McFall and colleagues (2019) found that education discriminated between stable memory aging and normal memory aging classes for Young-Old and Old-Old adults. Furthermore, their results also indicated that high education and high cognitive activity discriminated between stable memory aging and declining memory aging classes across both age strata. Although stable memory aging does not necessarily denote cognitive resilience, it is probable that some of the individuals in their stable memory aging class have various risk factors for AD. Therefore, factors discriminating stable memory aging from normal memory aging may be relevant to consider in the context of cognitive resilience. In the present chapter, education was found to discriminate resilient from non-resilient subclasses only for the memory and EF domains. Notably, these are the two of the most age-sensitive cognitive functions, in which decline is salient and detectable in the preclinical phases of AD (Mortamais et al., 2017). Therefore, it is plausible that EF and memory domains would be selectively sensitive to factors that have influences on neural development, such as education in the early life.

Age is a key risk factor for cognitive decline and neurodegenerative diseases (Guerreiro & Bras, 2015). Results from the present chapter indicated that younger age was a predictor of EF resilience to frailty. Notably, a recent study by Cabellero and colleagues (2020) investigated predictors of EF trajectories in older adults and found that age was a significant predictor of membership in the highest performing subclass, similar to the results in this chapter.

Mechanistically, age-related losses in prefrontal cortex (PFC) volume and cortical thickness may be responsible for this association. Greater PFC volume and thickness is associated with higher performance on various EF tasks (Yuan & Raz, 2014). Thus, age-related deterioration of the PFC may influence EF resilience to the effects of frailty.

While our results indicated that current alcohol use was associated with memory resilience to frailty, mixed evidence exists for the interplay between cognitive function and alcohol use. For example, a reverse u-shaped pattern has been established, as several studies provide evidence that moderate alcohol use is associated with a reduced risk of cognitive decline and heavy alcohol use is associated with faster cognitive decline (Neafsey & Collins, 2011; Richard et al., 2017; Sabia et al., 2014). However, it has been contested that the relationship may be domain specific, with an inverted u-shape pattern indicated for memory, and a linear pattern indicated for global cognition and EF (Reas, Laughlin, Kritz-Silverstein, Barrett-Connor, & McEvoy, 2016). As the present chapter did not examine the amount of alcohol consumed, future research could examine the dose-dependent relationship relative to cognitive resilience.

Marital status is an important risk/protective factor for cognitive decline and impairment but is often overlooked (Liu, Zhang, Burgard, & Needham, 2019; Liu, Zhang, Choi, & Langa, 2020). Our results indicate that being married contributed to memory resilience to frailty. This effect could be due to the psychosocial benefits (e.g., social activity, cognitive activity, and emotional support) associated with having a partner throughout the lifespan.

Sex is an important factor influencing cognitive performance and change (McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016). It is well established that females have a higher risk for AD and dementia (Podcasy & Epperson, 2016). Additionally, previous research has shown that females have higher levels of frailty than males and high frailty levels are predictive of

lower memory performance and more memory decline over time for females (Gordon et al., 2017; Thibeau, McDermott, McFall, Rockwood, & Dixon, 2019). To add further complexity, McDermott and colleagues found that memory resilience was predicted by a greater number and wider breadth of factors for females than males. Moreover, McFall and colleagues (2019) indicated that female sex discriminated between the stable memory aging and normal memory aging classes, and between stable memory aging and declining memory aging classes across both Young-Old and Old-Old age strata. Interestingly, the results of the present chapter indicated female sex was a significant predictor of memory resilience, indicating existence of a small subsample of females that are resilient to the effects of frailty on memory performance and change. While the area under the receiver operating characteristic curve of this RFA was small (C = 0.55), this prediction result indicates two main important considerations. First, while there was a previously established overall effect of frailty on memory performance and change for females (Thibeau et al., 2019), there may be heterogeneity within this effect that is detected only when examining the subsample of highly frail individuals. Therefore, when examining frailty and memory trajectories in older females, one should take into consideration the interindividual variability within these developmental pathways. Second, a subsequent RFA was run on the subsample of females to further elucidate this interesting effect. Results indicated that several predictors distinguished memory resilient from non-resilient females (C = 0.62, 95% CI [0.48, 0.76]). These factors were high education, *APOE* non-risk status, being married, living with someone, alcohol use, and high cognitive activity. Notably, in comparison to McDermott and colleagues (2017), all of these factors except for alcohol use and *APOE* non-risk status were common to the classes of females who had resilience to genetic risk for AD. We note that this additional analysis was also conducted with the subsample of males; however, there were not

enough participants to run the model (n = 21). Taken together, this indicates that there are several factors that can foster memory resilience in the face of frailty for females, offering further refinement on the sex effect of frailty on memory performance and change (Thibeau et al., 2019).

Our results also suggest that while some predictors of cognitive resilience are generalizable across cognitive domains, such as high cognitive activity, other predictors have domain-specific influences. McDermott and colleagues (2017) and Kaup and colleagues (2015) both noted variability in prediction patterns of resilience based on subgroups of non-modifiable factors such as genetic risk, race, and sex. As this area of research expands and cognitive resilience to AD risk is examined across more studies, we may find that several factors are found to be selectively predictive of cognitive resilience (i.e., specific to risk factor or specific to cognitive domain). In the present research, we note that some factors did not predict cognitive resilience as expected. For example, social and volunteer activity were not found to be predictive of cognitive resilience to frailty, despite being robust predictors of memory resilience (McDermott et al., 2017). Additionally, *BDNF* has been related to neuroprotection through synaptic plasticity and the reduction of inflammation (Markar et al 2008; Martinowich et al., 2007). *BDNF* has also been identified as a potential mediator of resilience (Karatsoreos & McEwan, 2013). Additionally, plasma BDNF levels have been found to differ in non-frail and frail individuals (Coelho et al., 2011), and reduced plasma BDNF levels associated with frailty have been related to the single nucleotide polymorphism *BDNF* (Ingles et al., 2016). Thus, we expected *BDNF* genetic status to be a predictive factor discriminating between resilient and non-resilient individuals. However, our results did not support this expected result. Also, *APOE* genetic status has been previously identified as a moderator of the effect of frailty on memory decline. Specifically, frailty has been found to have a deleterious effect on memory decline only

for *APOE* risk carriers (Chapter Two: Thibeau et al., 2019). Additionally, there were differential predictive factors for cognitive resilience to *APOE* genetic risk status when stratified by sex and race (Kaup et al., 2015; McDermott et al., 2017). Taken together, we expected *APOE* genetic risk status to be predictive of cognitive resilience to frailty. However, in the present chapter, *APOE* non-risk status was predictive only of memory resilience to frailty for females, but not for the other two cognitive domains. Future research could examine this interesting sex-specific effect to see if *APOE* non-risk status is a predictive factor of EF or speed resilience as well.

There are several strengths and limitations to this research. Regarding limitations, first, the class of frail individuals comprised a relatively small sub-sample (n = 95). However, this relatively frail class constituted about 15% of the study sample and was thus comparable in proportion to a recently estimated occurrence of frailty in non-demented, community-dwelling older adult samples (also 15%; Bandeen-Roche et al., 2015). From this frail class, we initiated the classification analyses that produced the cognitively resilient and non-resilient sub-classifications. Although the analyses produced meaningful results, a larger relatively frail class would have been preferable. Second, the fit indicators (area under the Receiver Operating Characteristic curve) for the RFAs predicting memory and speed resilience to frailty were relatively small (C = 0.55 and 0.57, respectively). Such values are associated with models characterized as having between small to medium effect sizes (i.e., d = 0.21 and 0.26, respectively) (Rice & Harris, 2005; Salgado, 2018). This result indicates that our pool of 12 predictors were moderately successful at discriminating the EF resilient from non-resilient subclasses (C = 0.69), but that there could be room for improvement in the discrimination for the memory and speed resilience subclasses. Notably, when memory resilience was considered only in the context of females, the C-statistic was 0.62, indicating significantly better discrimination

than when the model was conducted with females and males combined. We note that this analysis could not be applied only in the context of males, due to small cell sizes (resilient males $n = 10$; non-resilient males $n = 11$). In a cognitive resilience study with a similar approach but different form of resilience (to genetic risk), McDermott and colleagues (2017) had 22 predictors and found C-statistics of between 0.73 – 0.78 (females) and 0.69 – 0.72 (males) prior to a data augmentation approach. After the data augmentation approach was used to balance their cell sizes (i.e., Synthetic Minority Oversampling Technique; SMOTE; Chawla, Bowyer, Hall & Kegelmeyer, 2002), the AUC values increased to 0.82 – 0.91 (females) and 0.77 – 0.78 (males). Upon consideration, future research could examine whether a data augmentation approach would yield higher fit indices for cognitive resilience to frailty. Alternately, including more predictors may also lead to higher discrimination with RFA, thus bringing us to the third limitation. The number of predictors we were able to test was limited because of the comprehensive 50-item frailty index. In the foundational steps of this chapter, we made sure that the predictors considered were not also included in the frailty index, which resulted in fewer variables available to use for our study. Specifically, when compared with the 22 predictors used in McDermott and colleagues (2017), nine predictors they used were already included in the frailty index and could not be used to discriminate cognitive resilience to frailty. These variables were walking time, PP, turning time, peak expiratory flow, grip strength, depressive symptoms, physical activity, BMI, and anti-inflammatory medication. In order to examine a larger number of predictors of cognitive resilience to frailty, with the potential of having higher discrimination values for the RFA models, future VLS research may consider a FI with fewer indicators. Notably, 30-70 item FIs have been found to provide robust risk estimates, so a FI with 30 items may be a feasible target for future research (Cesari et al., 2014; Mitnitski, Graham, Mogilner, & Rockwood, 2002;

Mitnitski, Mogilner, & Rockwood, 2001). Fourth, some of the resilient or non-resilient cell sizes were relatively small (e.g., n = 29), however, we used RFA for the analysis, which is suitable for testing multiple predictors even with small sample sizes (Strobl, Hothron, et al., 2009). Fifth, participants were selected to be relatively healthy and non-demented, which may not be representative of all older adults. Notably, however, within this sample we had variable distributions within frailty and cognitive performance, representative of the range of variability within non-demented community dwelling western populations. Sixth, although frailty and the cognitive domains were represented with growth models based on multiple data collection points, predictors of resilience were tested at baseline. Testing these predictions against second or third data collection points could be an interesting examination of robustness of these predictors.

Regarding strengths, we used an accelerated longitudinal design, spanning a 40-year band of aging, which allowed us a robust examination of frailty and cognitive trajectories in older adults. With this approach, we used age as the metric of change which enabled us to cover this broad band of aging in a shorter period and examine individualized trajectories of frailty and cognitive performance over time. Second, we note the novel focus of this chapter: resilience to frailty. To quantify this novel concept, we used a 50-item frailty index, and multi-item latent cognitive variables. The classification of subgroups within cognitive and frailty performance and subsequent cognitive resilience was based on level and performance across these robust indicators. Third, we used modern data-driven statistical approaches (LCGA and RFA) to examine our research goals. These advanced modern approaches provide objective classification and high prediction accuracy within this non-demented sample of older adults. Additionally, one advantage of using RFA is that all predictors are evaluated and compared in a quantitatively

competitive context. This evaluation produces a robust estimation of the precise order of predictive factors discriminating between the subclasses of resilience and non-resilience.

In conclusion, this chapter indicates that older adults with varying frailty trajectories can be objectively classified into two phenotypes, frail and non-frail. Additionally, this chapter quantified the discordance between higher cognitive function and frailty. Specifically, cognitive resilience was defined as being frail and having higher levels and sustained or slightly declining cognitive performance. Notably, we examined cognitive resilience across three domains of cognition, namely memory, speed, and EF. As resilience is a multidimensional phenomenon, arising from the combination or interaction of several protective resources and risk factors, we examined whether several factors were predictors of resilience to frailty. Our prediction analyses revealed that factors promoted as protective for AD (e.g., cognitive activity and education) distinguished cognitive resilience from non-resilience to frailty. Notably, as cognitive resilience research progresses, many common factors which confer resilience may be identified across risk factors for AD. For example, it is possible that high cognitive activity will foster cognitive resilience to multiple types of risk for cognitive decline. In contrast, our results also indicate that profiles of resilience may also be unique to the risk factor being examined. Accordingly, identifying common predictors of cognitive resilience to AD risk has the potential for generalized recommendations to be made for promoting brain and cognitive health for older adults. Moreover, detecting unique factors that are predictive of resilience to specific types of AD risk fosters an opportunity for precision intervention for older adults (Dixon & Lachman, 2019). Therefore, increasing cognitive resilience, considering the multi-dimensional health challenges faced by older adults, offers an opportunity for multifactorial intervention and assistance for this particularly vulnerable population.

Table 3-1

Baseline Descriptive Statistics for Entire Sample, by Frail Class, and Cognitive Resilience Status

			Cognitive Resilience Status Within the Frail Class					
	Whole Sample	Frail Class	Memory Resilience	Memory Non-Resilience	Speed Resilience	Speed Non-Resilience	EF Resilience	EF Non-Resilience
	n = 632	*n* = 95	n = 58	n = 37	*n* = 52	*n* = 43	*n* = 66	*n* = 29
Age (years)	70.65 (8.70)	70.62 (7.22)	70.60 (7.41)	70.63 (7.02)	70.98 (7.42)	70.18 (7.04)	69.20 (7.16)	73.84 (6.35)
Sex (% female)	66.90	77.90	82.80	70.30	78.80	76.70	77.30	79.30
Education (years)	15.24 (2.97)	14.85 (2.89)	15.29 (2.92)	14.16 (2.73)	15.13 (3.06)	14.51 (2.67)	15.21 (2.81)	14.03 (2.96)
Frailty Score	0.13 (0.07)	0.23 (0.07)	0.22 (0.06)	0.24 (0.08)	0.22 (0.06)	0.23 (0.08)	0.22 (0.06)	0.25 (0.08)
Memory Score	-0.07 (3.67)	-0.55 (3.14)	1.25 (1.98)	-3.36 (2.48)	0.17 (2.81)	-1.41 (3.32)	0.49 (2.55)	-2.91 (3.08)
Speed Score	-0.42 (7.08)	-0.86 (6.33)	0.75 (4.40)	-3.38 (7.97)	3.10 (3.53)	-5.64 (5.66)	1.47 (4.56)	-6.15 (6.69)
EF Score	-0.06 (0.76)	-0.21 (0.68)	0.02 (0.51)	-0.58 (0.75)	-0.02 (0.53)	-0.45 (0.76)	0.16 (0.32)	-1.06 (0.48)
MMSE	28.73 (1.21)	28.71 (1.14)	28.81 (1.05)	28.53 (1.27)	28.60 (1.11)	28.85 (1.15)	28.67 (1.11)	28.80 (1.23)

Note. Results presented as *Mean (Standard Deviation)* unless otherwise stated. Abbreviations: EF, executive function; MMSE, Mini-mental state examination score.

Table 3-2
List of Variables Used to Construct the 50-Item Frailty Index

	Frailty Measures	Coding
SR	Stroke	0 = no 0.33 = yes, not serious 0.67 = yes, moderately serious 1 = yes, very serious
	Thyroid condition	
	Arthritis (rheumatoid and/or osteo-)	
	Osteoporosis	
	Cancer	
	Asthma	
	Migraines	
	Stomach ulcer	
	Kidney or bladder trouble	
	Gastrointestinal problems (colitis/diverticulitis, gall bladder trouble, and/or liver trouble)	
	Bronchitis or emphysema	
	Diabetes	
	High blood pressure	
	Sex-related health problems (i.e., gynecological problems or prostate problems)	
	Anaemia	
	Drug and/or alcohol dependence	
	Spinal condition and/or back trouble	

	Hardening of arteries (i.e., atherosclerosis)	
	Heart trouble	
	Other conditions (up to three)	
SR	Number of medications	0 = 0-3; 0.5 = 4-7; 1 = 8+
SR	Subjective health relative to a perfect state of health	0 = very good 0.25 = good 0.50 = fair 0.75 = poor 1 = very poor
SR	Eyesight relative to age group	
	Hearing relative to age group	
SR	Health has affected ability to do chores	0 = no change, improved, N/A 0.25 = slightly reduced 0.50 = moderately reduced 0.75 = drastically reduced 1 = gave up doing activity
	Health has affected ability to get around town	
	Health has affected ability to do mental recreational activities	
	Health has affected ability to do physical recreational activities	
	Health has affected ability to do hobbies	
	Health has affected ability to socialize	
	Health has affected ability to travel	
SR	Stay at home but in chair most of the time	0 = no; 1 = yes
SR	Number of times sick in bed all day in the past year	0 = 0-3; 1 = 4+
SR	Number of times confined to hospital in the past year	0 = 0; 0.5 = 1-2; 3+ = 1

SR	Feeling short of breath	0 = no; 1 = yes
SR	Use of a walker, cane, or wheelchair	0 = no; 1 = yes
M	Resting heart rate (bpm)	0 = 60-99; 1 = <60 or 100+
M	Pulse pressure (mmHg)	0 = 52-63 ; 0.5 = 64-75.9; 1 = 76+
M	Peak expiratory flow (L/min)	Men: 0 = >340; 1 = ≤340 Women: 0 = >310; 1 = ≤310
M	Body mass index (kg/m^2)	0 = 18.5-25 0.5 = 25-<30 1= <18.5 or ≥30
M	Grip strength (kg)	Men: For BMI ≤24, GS ≤29 For BMI 24.1-28, GS ≤30 For BMI >28, GS ≤32 Women: For BMI ≤23, GS ≤17 For BMI 23.1-26, GS ≤17.3 For BMI 26.1-29, GS ≤18 For BMI >29, GS ≤21
M	Timed walk	0 = ≤10s; 1 = >10s

M	Timed turn	0 = < 90th percentile 1 = within 90th percentile
M	Finger dexterity	0 = < 90th percentile 1 = within 90th percentile
SR	CES-D "during the past week, my sleep was restless"	0 = rarely or none of the time 0.33 = some or a little of the time 0.67 = occasionally or a moderate amount of the time 1 = most or all of the time
SR	CES-D "during the past week, I felt depressed"	
SR	CES-D "during the past week, I felt lonely"	
SR	CES-D "during the past week, I could not get going"	
SR	Bradburn negative affect (restless, lonely, bored, depressed, upset due to criticism)	0 = no to all 0.2 = yes to one 0.4 = yes to two 0.6 = yes to three 0.8 = yes to four 1 = yes to all
SR	Physical activity at least 2-3 times per week	0 = yes; 1 = no

Note. SR = Self-reported; M = measured; CES-D = Center for Epidemiological Studies Depression Scale

Table 3-3

Correlations Between Predictor Variables

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	1												
2. Education	0.115	1											
3. Sex	0.085	0.186	1										
4. Marital status	-0.043	-0.139	**-0.217***	1									
5. Living status	-0.033	0.113	**0.290****	**0.535****	1								
6. Pets	-0.179	0.011	0.011	-0.011	0.073	1							
7. Smoke	-0.072	0.135	0.049	-0.021	-0.094	0.158	1						
8. Drink	0.044	-0.017	0.026	0.095	0.146	0.089	**-0.202***	1					
9. Social Activity	-0.044	0.172	-0.075	-0.060	0.050	-0.007	-0.136	-0.061	1				
10. Cognitive	-0.168	**0.352****	0.191	**-0.206***	0.107	0.088	-0.130	0.083	**0.499****	1			
11. Volunteer	0.040	0.105	-0.071	0.038	0.070	-0.115	-0.073	-0.110	**0.676****	**0.352****	1		
12. *APOE*	-0.072	0.018	-0.007	0.025	-0.069	-0.125	-0.099	-0.039	0.116	0.114	0.075	1	
13. *BDNF*	-0.102	0.090	-0.119	0.118	0.028	0.020	0.138	-0.127	-0.123	-0.064	-0.069	**-0.221***	1

Note. Correlations were calculated for entire frail class (n = 95). Abbreviations: *APOE*, Apolipprotein E; *BDNF*, brain–derived neurotrophic factor. *Significant at $p < 0.05$, ** $p < 0.001$

Table 3-4

Goodness of Fit Indices for One to Three-Class Frailty Latent Growth Mixture Models

Model	Class	AIC	BIC	2LL	Entropy	Probability	Proportion	n
1	1	-4394.3	-4372.1	-4404.298	-	1	1	629
2*	**1**	**-4813.2**	**-4777.6**	**-4829.12**	**0.762**	**0.86**	**0.15**	**95**
	2	**-**	**-**	**-**	**-**	**0.95**	**0.85**	**534**
3	1	-4941.2	-4892.3	-4963.2	0.713	0.85	0.04	25
	2	-	-	-	-	0.88	0.71	446
	3	-	-	-	-	0.08	0.25	158

Note. *Preferred model. Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; -2LL, -2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimate model; *n*, sample size.

Table 3-5

Goodness of Fit Indices for One to Three Class Memory Latent Growth Mixture Models

Model	Class	AIC	BIC	2LL	Entropy	Probability	Proportion	n
1	1	1000.61	1013.00	-990.61	-	1	1	95
2*	**1**	**912.69**	**932.51**	**896.69**	**0.81**	**0.95**	**0.61**	**58**
	2	**-**	**-**	**-**	**-**	**0.93**	**0.39**	**37**
3	1	872.54	899.79	-850.54	0.87	0.93	0.38	35
	2	-	-	-	-	0.96	0.47	45
	3	-	-	-	-	0.91	0.16	15

Note. *Preferred model. -2LL, -2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimate model; *n*, sample size.

Table 3-6

Goodness of Fit Indices for One to Three Class Speed Latent Growth Mixture Models

Model	Class	AIC	BIC	2LL	Entropy	Probability	Proportion	n
1	1	1282.35	1294.68	-1272.36	-	1	1	95
2*	**1**	**1205.47**	**1185.75**	**-1169.74**	**0.85**	**0.97**	**0.55**	**52**
	2	**-**	**-**	**-**	**-**	**0.95**	**0.45**	**43**
3	1	1130.8	1157.93	-1108.8	0.88	0.94	0.46	44
	2	-	-	-	-	0.94	0.06	6
	3	-	-	-	-	0.98	0.43	41

Note. *Preferred model. Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; -2LL, -2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimate model; *n*, sample size.

Table 3-7

Goodness of Fit Indices for One to Three Class EF Latent Growth Mixture Models

Model	Class	AIC	BIC	2LL	Entropy	Probability	Proportion	n
1	1	399.76	412.09	-389.76	-	1	1	95
2*	**1**	**300.92**	**332.58**	**-284.92**	**0.91**	**0.97**	**0.31**	**29**
	2	**-**	**-**	**-**	**-**	**0.98**	**0.69**	**66**
3	1	240.98	268.1	-218.98	0.88	0.96	0.54	47
	2	-	-	-	-	0.95	0.1	9
	3	-	-	-	-	0.9	0.36	31

Note. * Preferred model. Abbreviations: EF, Executive Function; AIC, Akaike information criteria; BIC, Bayesian information criteria; -2LL, -2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimate model; *n*, sample size.

Table 3-8

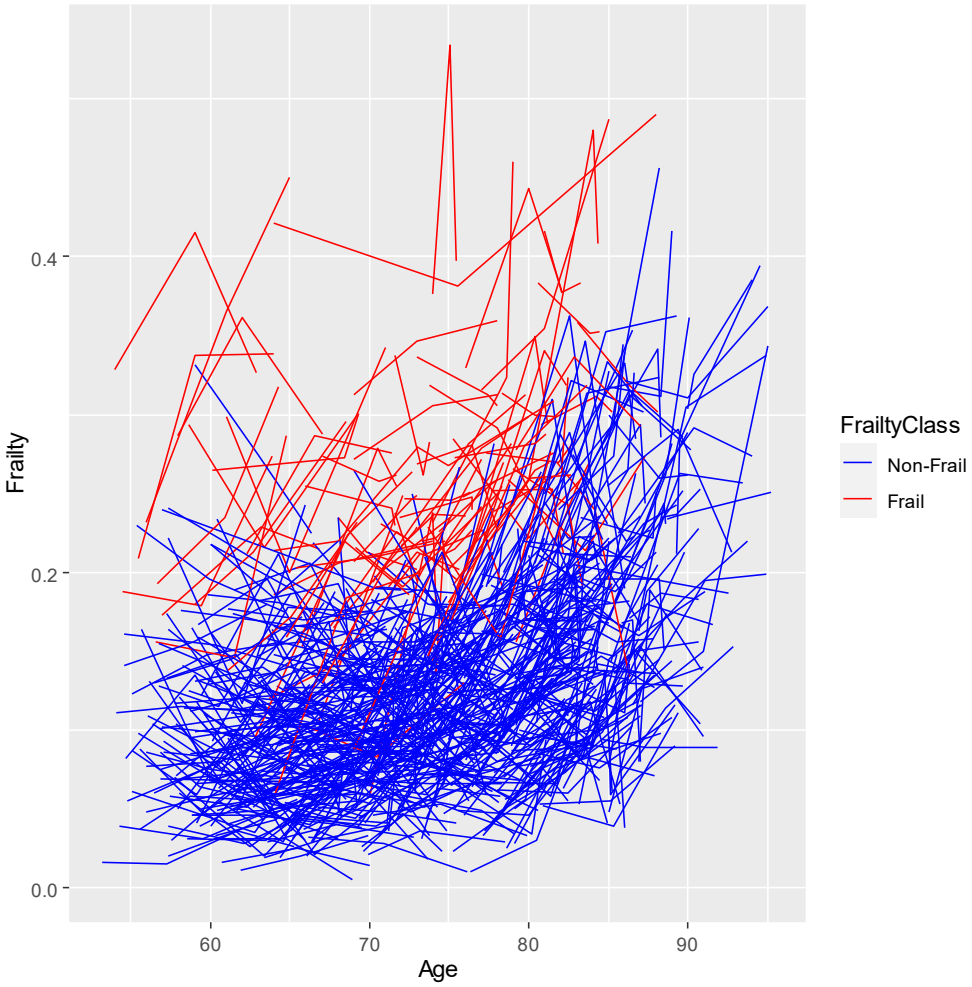
Generalizability of Predictors of Resilience to Frailty Across Cognitive Domains

	Memory	Speed	EF
Age			X
Education	X		X
Sex	X		
Marital Status	X		
Living Status			
Pet Ownership			
Alcohol Use	X		
Cognitive Activity	X	X	X
Social Activity			
Volunteer Activity			
APOE			
BDNF			

Note. Abbreviations: *APOE*, Apolipprotein E; *BDNF*, brain–derived neurotrophic factor.

Figure 3-1

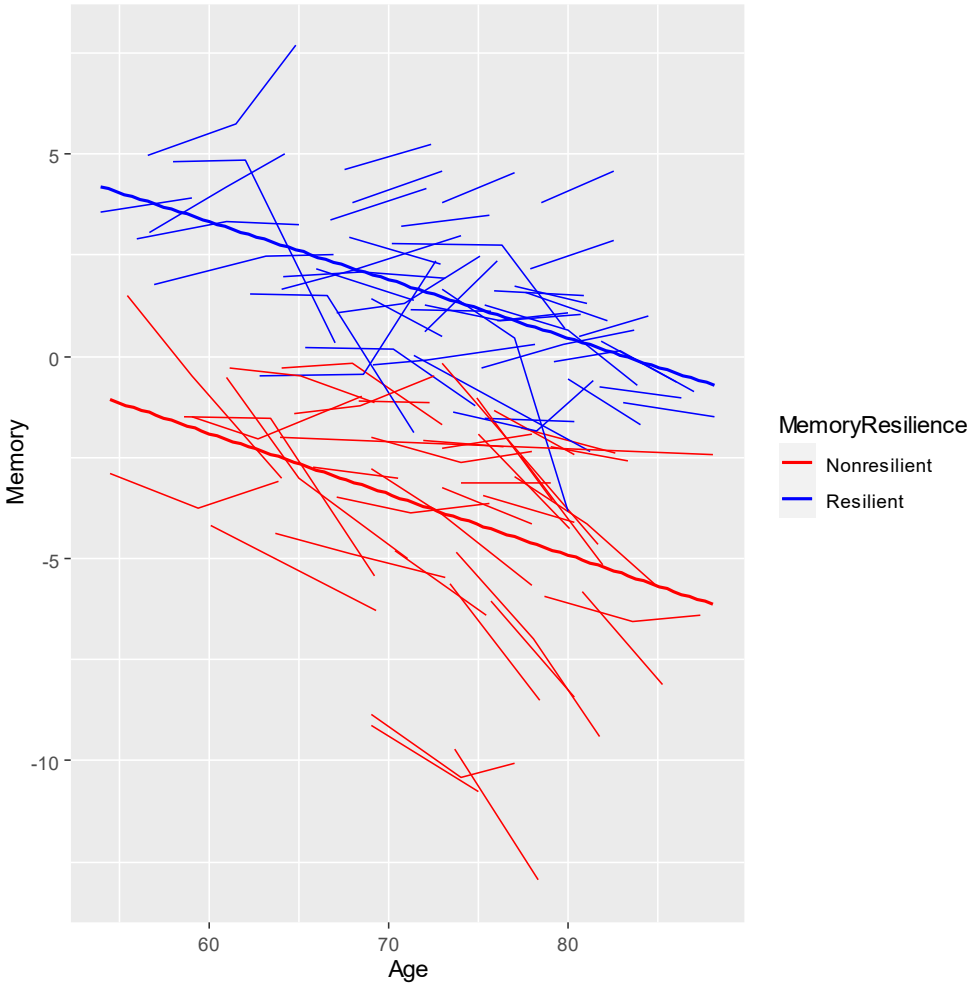
Frailty Trajectories Differentiated into a 2-Class Model



Note. Frailty distribution divided into 2-classes (i.e., frail n = 95, non-frail n = 534) based on level and slope with latent class growth analysis. Blue lines represent non-frail, red lines represent frailty.

Figure 3-2

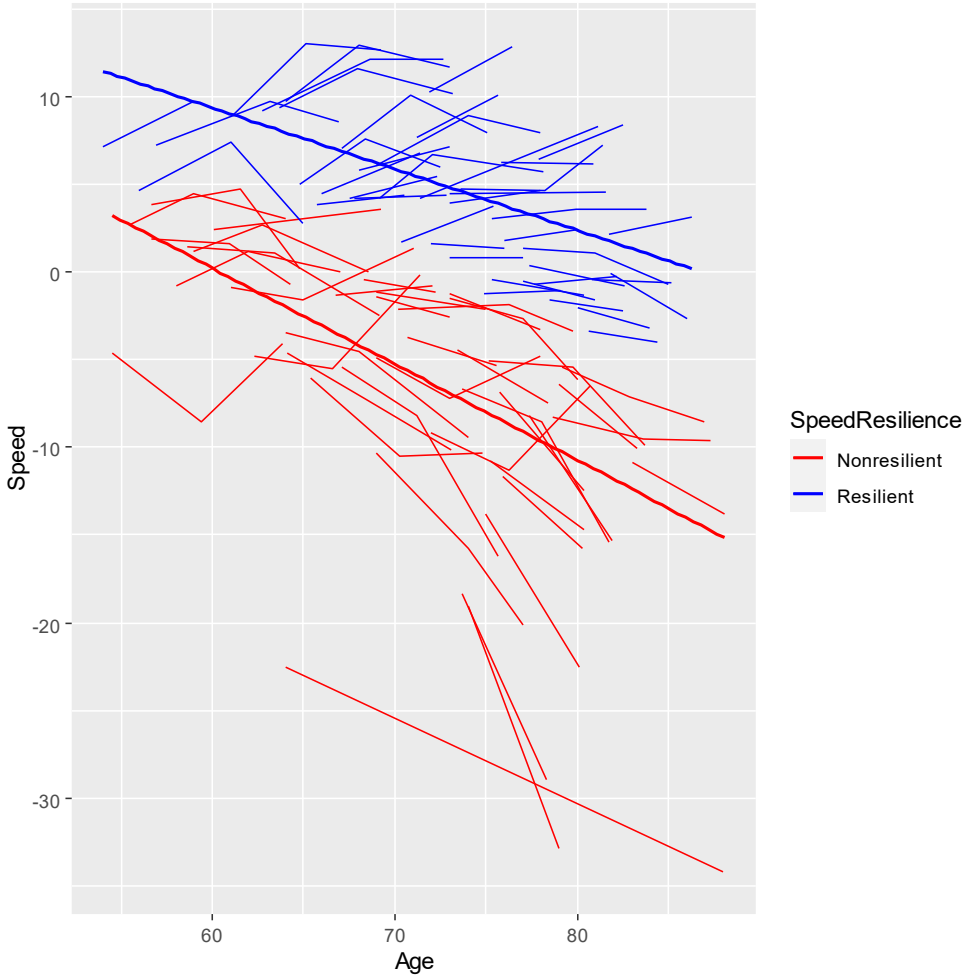
Memory Trajectories Differentiated into a 2-Class Model



Note. Memory trajectories within the frail class, divided into two subclasses based on level and slope of memory with latent class growth analysis. Blue lines represent higher performing (i.e., memory resilience to frailty, $n = 58$), while red lines represent lower performance (i.e., non-resilience to frailty, $n = 37$).

Figure 3-3

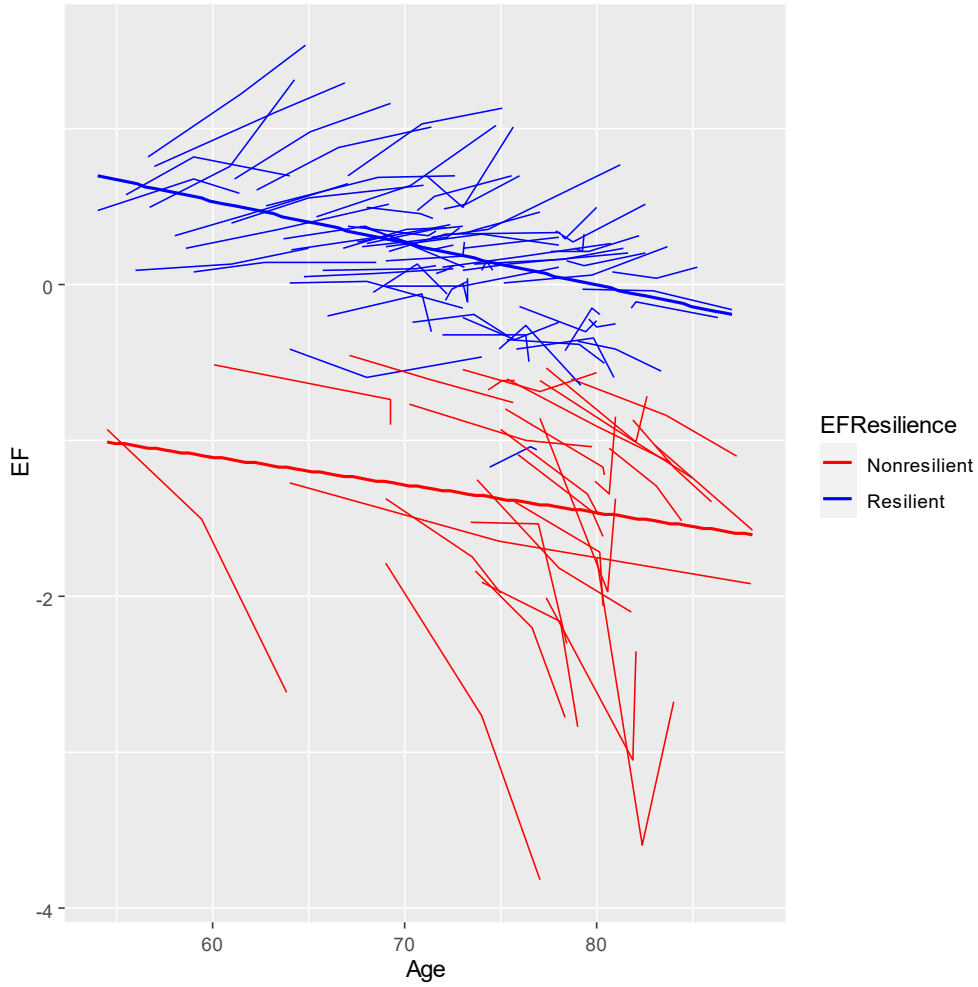
Speed Trajectories Differentiated into a 2-Class Model



Note. Speed trajectories empirically classified into a 2-subclass model based on speed performance and change. Blue lines represent higher performance (i.e., speed resilience to frailty, $n = 52$), while red lines indicate lower performance (i.e., non-resilience to frailty, $n = 43$).

Figure 3-4

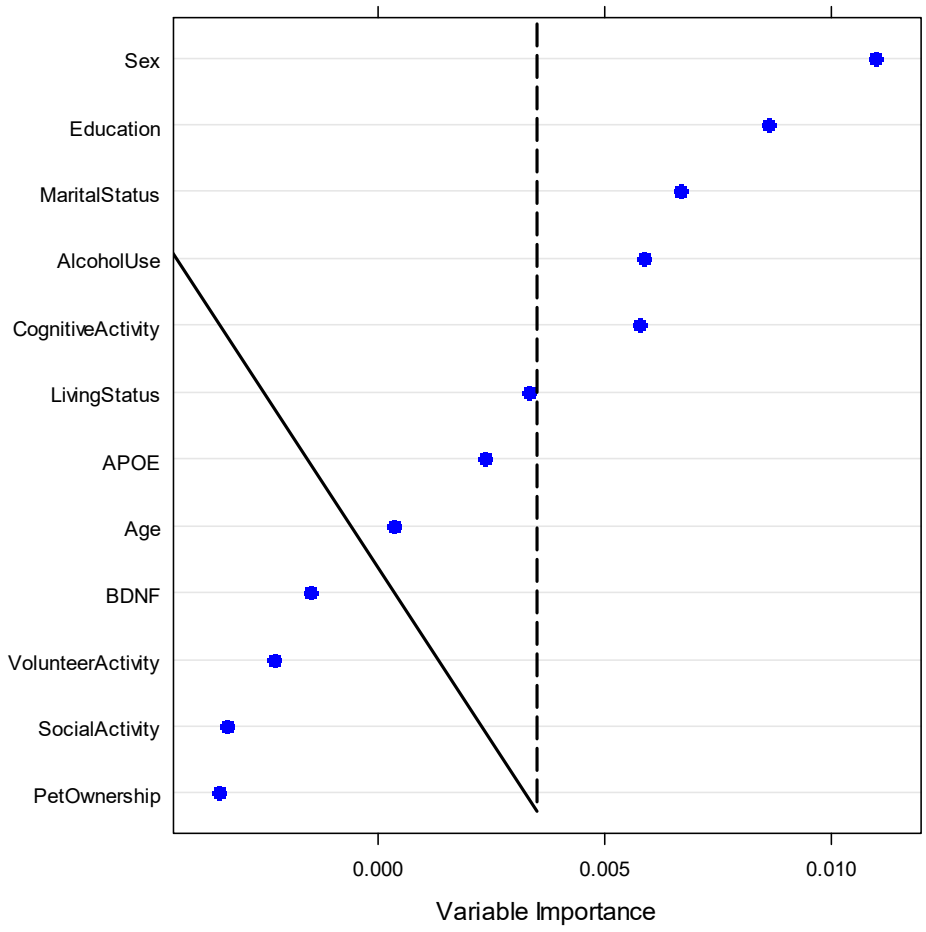
Executive Function (EF) Trajectories Differentiated into a 2-Class Model



Note. EF trajectories within the frail class, divided into two subclasses (resilient, non-resilient) based on level and slope. Blue lines represent higher performance (i.e., EF resilience to frailty, *n* = 66), while red lines indicate lower performance (i.e., non-resilient to frailty, *n* = 29).

Figure 3-5

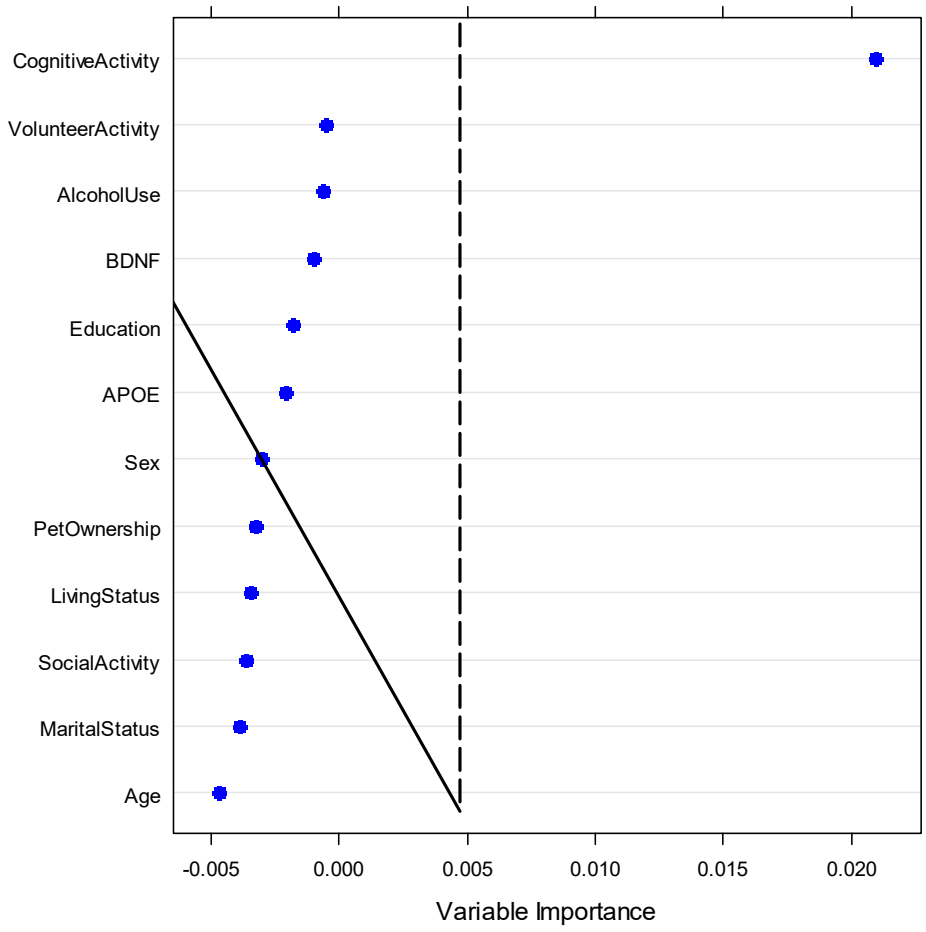
Relative Importance of Predictors of Memory Resilience to Frailty



Note. Predictors of memory resilience versus non-resilience to frailty. Dotted line represents cut-off values for variable importance. Variable importance was calculated based on the mean decrease in accuracy (C = 0.55; 95% CI [0.39 – 0.63]; n = 95). Predictors to the right of the vertical line have the best permutation accuracy importance. Abbreviations: *BDNF*, brain–derived neurotrophic factor; *APOE*, Apolipoprotein.

Figure 3-6

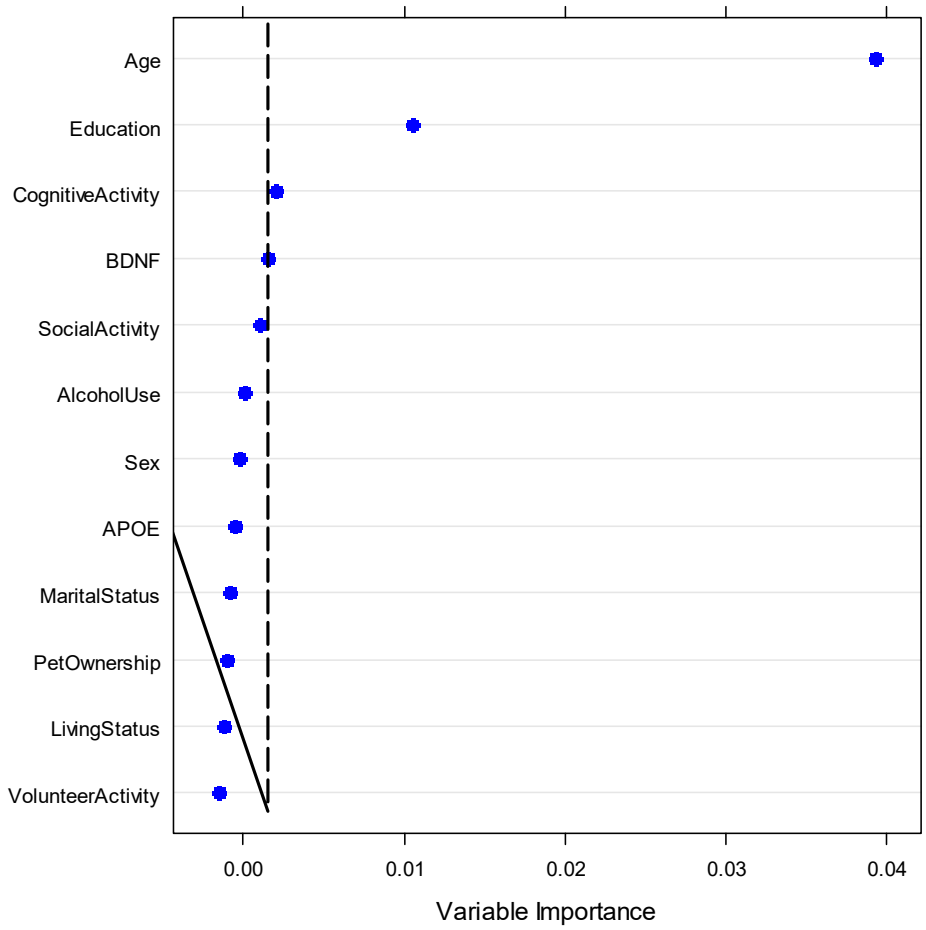
Relative Importance of Predictors of Speed Resilience to Frailty



Note. Predictors of speed resilience versus non-resilience to frailty. Dotted line represents cut-off values for variable importance. Variable importance was calculated based on the mean decrease in accuracy (C = 0.57; 95% CI [0.49 – 0.68]; n = 95). Predictors to the right of the vertical line have the best permutation accuracy importance. Abbreviations: *BDNF*, brain–derived neurotrophic factor; *APOE*, Apolipoprotein.

Figure 3-7

Relative Importance of Predictors of Executive Function Resilience to Frailty



Note. Predictors of EF resilience versus non-resilience to frailty. Dotted line represents cut-off values for variable importance. Variable importance was calculated based on the mean decrease in accuracy (C = 0.69; 95% CI [0.56 – 0.79]; n = 95). Predictors to the right of the vertical line have the best permutation accuracy importance. Abbreviations: *BDNF*, brain–derived neurotrophic factor; *APOE*, Apolipoprotein.

Chapter Four: Cognitive Resilience: The Crossroads of Low Mobility and High Cognitive Performance

As the world demographics shift, the percentage of people over the age of 65 is estimated to nearly double over the next 25 years (United Nations, 2019). While not a normal part of aging, cognitive impairment and dementia present a major challenge to healthcare (Shah et al., 2016). Dementia is a significant cause of dependence and disability, and has substantial economic costs (World Health Organization, 2019). Recently, dementia risk reduction was identified as an important target for the public health response to dementia (World Health Organization, 2019). In parallel, several studies have identified risk factors that are associated with cognitive decline, impairment, and dementia (Anstey, 2014; Livingston et al., 2017). Notably, risk-reduction is a feasible target for many modifiable risk factors, such as smoking or a sedentary lifestyle. However, some risk factors may not be modifiable or are the result of multisystem physiological decline and therefore not be amendable to such strategies. Therefore, a resilience framework may be warranted.

Resilience in aging has been used to convey the concept that individuals can maintain or regain sustained levels of functioning despite significant risk factors in their lives (Staudinger & Greve, 2015). With regards to cognitive aging, resilience may be conceptualized as the ability to maintain cognitive performance over time, despite the presence of risk factors that increase the likelihood of decline and impairment (Anstey & Dixon, in press). Newly emerging research has characterized cognitive resilience as relatively high cognitive performance and stable change trajectories despite significant AD genetic risk (Kaup et al., 2015; McDermott et al., 2017). Of note, genetic risk is one of many factors that have been identified to have a negative influence on cognitive performance and decline.

Mobility deficits increase with advancing age and are the cardinal signs of further functional impairment (Rantakokko, Mänty, & Rantanen, 2013). Mobility is a core component of functional health that influences cognitive trajectories across midlife and older adulthood and has a strong predictive value for disability and morbidity (Ferrucci et al., 2016). Maintaining a high level of mobility is associated with increased protection against age-related structural brain changes and subsequent declines in EF, memory, and processing speed (Demnitz et al., 2017; Zhao, Tranovich, & Wright, 2014). A recent review examined the relationship with mobility and cognition across several domains and concluded that better mobility was associated with better performance in global cognition, memory, EF, and processing speed (Demnitz et al., 2017).

In contrast, the slowing of gait speed has been identified as a marker of cognitive decline and impairment (Montero-Odasso, Verghese, Beauchet, & Hausdorff, 2012; Rosano & Snitz, 2018). Declines in multisystem mobility performance measures, such as walking speed and tests of balance, are consistently associated with lower quality of life, adverse health outcomes, lower cognitive performance, transitions between normal cognition to mild cognitive impairment, increased risk for dementia and mortality (Cooper, Kuh, & Hardy, 2010; Grande et al., 2019; Hoogendijk et al, 2020; Perera et al., 2016; Studenski et al., 2011; Thibeau et al., 2017; Thibeau et al., 2019). Moreover, mobility limitations, impairment, and gait abnormalities are all indicators of altered brain function such as cognitive decline, mild cognitive impairment, and dementia (Hoogendijk et al., 2020; Tian et al., 2017; Varma et al., 2016; Verghese et al., 2008). In fact, the combination of slow gait and cognitive complaints has been termed ‘motoric cognitive risk syndrome’ (MCR) (Ayers, Verghese, & Allali, 2015). Conversely, it may be possible that older adults with low mobility levels can maintain high cognitive performance, displaying cognitive resilience to low mobility. As such, the present chapter examines whether

older adults with low mobility levels can maintain their cognitive performance, displaying cognitive resilience.

Cognitive resilience may be determined by a constellation of resources that contribute to optimal cognitive functioning despite the presence of AD risk (Anstey & Dixon, in press; Staudinger & Greve, 2015). Emerging research in this area suggests that certain factors help protect older adults from the detrimental cognitive effects of *APOE* genetic risk (Kaup et al., 2015; McDermott et al., 2017). For example, high cognitive activity and high education have been found to contribute to cognitive resilience to *APOE* genetic risk (Kaup et al., 2015; McDermott et al., 2017). Upon consideration, a comparable phenomenon may exist when considering low mobility. Specifically, factors from multiple domains may differentiate cognitive resilience to low mobility from non-resilience. Furthermore, this conceptualization of cognitive resilience to low mobility may be counter to MCR; resilience would be characterized in non-demented older adults as poor mobility (i.e., slow gait speed and poor balance) yet maintained cognitive trajectories.

Whilst an important phenomenon, the concept of cognitive resilience to low mobility provides considerable benefit for older adults. Identifying and stabilizing, or even increasing conditions that are protective to cognitive functioning despite mobility impairment has potential for delaying the onset of dementia. Moreover, empirical evidence on cognitive resilience has the potential to provide the foundation for interventions targeted at increasing factors which foster resilience to AD risk.

Research Goals

This chapter had two main aims. First, cognitive resilience to low mobility was defined and characterized across three domains of cognition, including memory, speed, and EF. Second,

22 factors from lifestyle, demographic, health, and genetic domains were examined as predictors of cognitive resilience to low mobility. We assembled a distribution of individualized mobility trajectories covering a 40-year band of aging (53 – 95 years). We used data-driven analytics to investigate three research goals (RGs). For RG1 we used LCGA to classify mobility classes based on an algorithm of level and slope of the individualized mobility trajectories. For RG2, we selected the low mobility class identified in RG1 and applied LCGA to each of three cognitive domain trajectory distributions. These analyses served to discriminate two subclasses of cognitive trajectories, with the higher subclass reflecting cognitive resilience to low mobility and the lower subclass reflecting non-resilient trajectories. These analyses were conducted separately for the three cognitive domains. For RG3, RFA was used to identify salient predictors that discriminated the cognitively resilient from the non-resilient subclass. The same pool of 22 potential predictors was used in the models for each cognitive domain.

Methods

Participants

Participants were community-dwelling older adult volunteers of the VLS. The VLS is an ongoing Canadian, large-scale, long-term, multi-cohort investigation of human aging, impairment, and dementia as influenced by genetic, biomedical, biological, health, lifestyle, and other factors (Dixon & de Frias, 2004). Three main sequential samples (initially aged 53 – 95 years) are followed at about 4-year intervals (M = 4.4-year interval). All participants provided written informed consent and all data collection procedures were in full and certified compliance (annually) with Health Research Ethics Board at the University of Alberta. As this research included examining genetic factors as predictive of cognitive resilience to low mobility, participants were limited to a source subsample who had provided biofluid for genotyping

between 2009 and 2011 (n = 695). This source subsample consisted of current subsets of three equivalent sequential cohorts, with present data collection occurring in the 2001 – 2015 period. The VLS cohorts were from Sample 1 (waves 6, 7, and 8), Sample 2 (waves 4 and 5), and Sample 3 (waves 1, 2, and 3). The total individualized duration is up to nine years (McFall et al., 2014). As this is the same sample used in the previous chapters in the dissertation, the exclusionary criteria included: (a) a diagnosis of AD or dementia (n = 0), (b) missing data at all three waves across any one of the 50 measures used to calculate the frailty index (n = 40), and (c) missing data at all three waves across any one of the four measures used to calculate the memory, speed, or EF latent variable (n = 23). The final study sample was comprised of 632 adults at baseline (M age = 70.7, range = 53.25 – 95.45; 66.9% female; see Table 2-1 for demographic information).

DNA Extraction and Genotyping. As previously described (McFall et al., 2014), the VLS collected saliva according to standard biofluid collection, stabilization, and preparation procedures from DNA Genotek. Genetic analyses included genotype categorization based on the presence or absence of the risk allele. *APOE* genotype was divided into dichotomous categories: ε4+ (risk) consisted of ε4ε4 and ε3/ε4 allele combinations and ε4- (non-risk) consisted of ε2ε2, ε2/ε3, and ε3ε3 allele combinations. For all analyses including *APOE*, we removed the genotype which combines the risk and protective alleles (ε2ε4; n = 30; McFall et al., 2014). The genotypic distribution for *APOE* was in Hardy-Weinberg equilibrium, $\chi 2 = 0.89$. Additionally, one other genetic factor associated with normal aging and mobility was included (i.e., BDNF). The *BDNF* genotype was divided into two categories, Met+ (risk) and Met- (non-risk). The genotypic distribution for *BDNF* was in Hardy-Weinberg equilibrium, $\chi 2 = 1.31$.

Measures

Mobility. Timed walk (gait measure) and timed turn (balance measure) have both been previously described elsewhere (MacDonald et al., 2017; Thibeau et al., 2017). These speed values (in seconds) were reverse-coded, and a composite mobility score was formed with unit-weighted z-scores of the two indicators. Higher scores indicated better mobility performance.

Measures for the Cognitive Latent Variables. The memory, speed, and EF tests included in the current chapter have been frequently used and validated with older adults in the VLS (and other studies). Citations indicate sources for established measurement attributes, structural characteristics, and sensitivity to health and neurological factors in older adult populations. For each set of manifest indicators, we calculated a latent variable to represent the construct (see Chapter Two: Thibeau et al., 2019 for the latent variable testing information and fit indices).

Episodic Memory. We calculated a robust latent variable comprised of four manifest indicators from two memory tasks (McFall et al., 2015): Word recall score on list 1, and score on list 2, Rey Auditory Verbal Learning Test list B1, and list A6.

Word Recall. Two lists of 30 content diverse English words were used to test immediate recall in a rotated design. Participants were given two minutes to study each list and five minutes to write as many words as they could recall (Dixon et al., 2004).

Rey Auditory Verbal Learning Test. A list of 15 nouns was read aloud and immediately recalled; this process was repeated for five trials (A1 – A5). Then a list (B1) of 15 unrelated nouns was read aloud and immediately recalled, measuring free recall. Then the participant was asked to recall the first list of nouns (A6), measuring recall after interference (Lezak, 1983).

Speed. We calculated a robust speed latent variable comprised of four manifest indicators from four speed tasks following established procedures (McFall et al., 2015). The tasks were

simple reaction time, choice reaction time, lexical decision, and sentence verification. Because each of the speed measures varied in complexity, we applied validated correction procedures with specific lower and upper limits as follows: (a) simple reaction time, 150 ms; (b) choice reaction time, 150 ms and 4000 ms; (b) lexical decision, 400 ms and 10000 ms; (c) sentence verification, 1000 ms and 20000 ms. Subsequent trials 3 standard deviations above the mean were removed.

Simple Reaction Time. Participants were presented with a warning stimulus (***) followed by a signal stimulus (+) in the middle of the computer screen and asked to press a key as quickly as possible when the signal stimulus appeared. Fifty trials were administered, and the latency of the 50 trials was used for analysis (Dixon et al., 2007).

Choice Reaction Time. A grid of (+) was presented on the computer screen, then after a 1000 ms delay one of the (+) was changed to a square, and participants were asked to indicate the location of the square using a matching arrangement of keys on the response console. The dependent measure was the average latency across 20 trials (Palmer, MacLeod, Hunt, & Davidson, 1985).

Lexical Decision. A string of five to seven letters were presented on the computer screen. Participants were asked to identify as quickly as possible whether the letters formed an English word. The average latency across 60 trials was used for analysis (Palmer et al., 1985).

Sentence Verification. A sentence was presented on the computer screen and participants were asked to identify as quickly as possible the plausibility of the sentence. The average latency across 50 trials was used for analysis (Palmer et al., 1985).

Executive Function (EF). We calculated a robust EF latent variable comprised of four manifest EF indicators (see Chapter Two, Thibeau et al., 2019 for fit indices): Hayling sentence completion test, Stroop test, Brixton spatial anticipation test, and Color trails test part two.

Hayling Sentence Completion. In section A, participants listened to 15 sentences read aloud with the last word missing, completing the sentence in a way that made sense and as quickly as possible. In section B, participants again listened to 15 sentences read aloud with the last word missing, completing the sentence quickly with a word that was unrelated or unconnected to the sentence. Response speed on both sections and errors within section B were used to create an overall scaled score (ranged from 1 [impaired] to 10 [very superior]) (Bielak et al., 2006; Burgess & Shallice, 1997).

Stroop. In part A, participants named the color of 24 dots (blue, green, red, or yellow) as quickly as possible. In part B, participants named the ink color of 24 words (e.g., "when"). In part C, participants named the ink color of color names (blue, green, red, or yellow) by ignoring the printed word and instead stating the color of the ink (e.g., if the word blue was printed in red ink, the correct answer was red). Scores were calculated from the interference index ([Part C time – Part A time]/Part A time) which reflects slowing in response to interference (Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997).

Brixton Spatial Anticipation Test. Participants deduced simple and changing patterns by predicting the movement of a blue dot among ten possible positions on a page, which followed patterns that came and went without warning. The total errors were recorded (maximum 54) and converted to scaled scores. An overall standardized scaled resulted in scores ranging from 1 (impaired) to 10 (very superior) (Bielak et al., 2006; Burgess & Shallice, 1997).

Color Trails Test. Participants connected the numbers 1 to 25 by alternating between pink and yellow circles while disregarding the numbers in circles of the alternate color. The latency score to complete the task was used for analysis (lower scores indicated better performance) (D'Elia, Satz, Uchiyama, & White, 1996).

Predictors from risk domains. A total of 22 predictive factors were included to discriminate cognitively resilient from non-resilient subclasses. These factors were included as baseline measurements from three risk domains: demographic, lifestyle, and genetic factors. Demographic factors included participants: (a) age in years, (b) marital status, (c) education (total years) (d) sex (male or female), (e) living status, and (f) pet ownership (yes or no). Lifestyle factors included: (a) everyday novel cognitive activity, (b) social activity, (c) volunteer activity, (d) physical activity, (e) alcohol use (yes or no), (f) current smoking status (smoker or non-smoker). Genetic factors included risk or non-risk status for the following genes: (a) *APOE* and (b) *BDNF*. Health factors included: (a) PP, (b) peak flow, (c) grip strength, (d) BMI, (e) anti-inflammatory medication, (f) subjective health, (g) depressive symptoms, and (h) diabetes. Bivariate correlations were examined for each of these predictors across each cognitive domain (see Table 4-2).

Statistical Analyses

Analyses pertaining to our RGs included LCGA through structural equation modeling using Mplus7 (Muthén & Muthén, 1998) and RFA using R 3.2.3 (R Development Core Team, 2015). Missing data was estimated in the growth models using robust maximum likelihood estimation. For the prediction analysis, missing predictor scores (0.02% overall, ranging from 0.01 – 0.04% across the predictor variables) were estimated using a random forest algorithm for

non-parametric imputation with the "missForest" package in R for the RFA (Stekhoven & Bühlmann, 2012; Waljee et al., 2013).

Foundational Analyses. Latent growth modeling was used to establish variability in intra-individual patterns of change over time for mobility. Growth models were tested in this order: (a) a fixed intercept model, which assumed no inter- or intra-individual variation, (b) a random intercept model, which modeled inter-individual variability in overall level but no intra-individual change, (c) a random intercept fixed slope model, which allowed inter-individual variability in level but assumes all individuals exhibited the same rate of change, and (d) a random intercept, random slope model which allowed inter-individual variability in level and change. The best growth model established variability in both level and change over time for mobility and was used in the analyses for RG1.

Analyses for RG1: LCGA for Mobility Classes. The established mobility growth model was used to perform LCGA on the full distribution of mobility trajectories data to determine mobility status based on an algorithm of individualized level and slope (Hayden et al., 2011; Jung & Wickrama, 2008; Nylund, Asparouhob, & Muthén, 2007; McFall et al., 2019; Pietrzak et al., 2015; Ram & Grimm, 2009). LCGA allows for data-driven, post-hoc classification of individual mobility trajectories using a latent categorical variable for class (Ram & Grimm, 2009). Three LCGA models were tested and compared: one, two, and three latent class mobility models. (Grimm, Ram, & Estabrook, 2016). For each class model tested, each model was a fully constrained growth model with a random intercept, random slope. The variance of both the intercept and slope were fixed to zero within the separate classes to determine differences (Berlin, Williams, & Parra, 2014). Model fit was determined using comparative fit indices (i.e., AIC, BIC, -2LL), entropy, proportion, and probability statistics (see Figure 4-1). The preferred

model was identified based on the following considerations: (a) low comparative fit indices, (b) high entropy value, (c) classes comprising a substantial proportion of the sample (>10% in each class), and (d) theoretical expectation.

Analyses for RG2: Cognitive Resilience to Low Mobility. Using the low mobility class established in RG1, the same LCGA procedure was used on individual memory trajectory data to determine resilience status classification (resilient to low mobility or non-resilient to low mobility) based on individualized level and slope trajectories. These steps were then repeated (separately) for speed and EF. For each latent cognitive variable, one-to-three class models were tested. Model fit was determined using comparative fit indices (i.e., AIC, BIC, -2LL), entropy, proportion, and probability statistics. The preferred model was identified based on the following considerations: (a) low comparative fit indices, (b) high entropy value, (c) classes comprising a substantial proportion of the sample (>10% in each class), and (d) theoretical expectation.

Analyses for RG3: Predictors of Cognitive Resilience to Low Mobility. RFA (R Development Core Team, 2015) was used to determine the most important (of 22) predictors of cognitively resilient or non-resilient status from four domains (i.e., genetic, demographic, health, and lifestyle). RFA is a supervised machine learning classification algorithm, which combines the predictions of many single classification and regression trees (*ntree*), each of which is based on a random sample of participants and prediction variables (*mtry*).

Using the Party Package in R 3.2.3 (R Development Core Team, 2015), our forest consisted of *ntree* = 5000 for good model stability, and at each potential split we evaluated a random sample of mtry = 5 predictors ($\sqrt{\#\ of\ predictors}$). Model strength was assessed as the area under the receiver operating characteristic curve (AUC; C-statistic), with values closer to one indicating better model strength. Relative to this chapter, the AUC equals the probability that

a randomly drawn score from the resilient subclass is higher than a randomly drawn score from the non-resilient subclass (Rice & Harris, 2005). When compared to Cohen's *d* (effect size) statistics, a C-statistic of 0.5 is considered to be chance, between 0.51 and 0.59 a small effect size, between 0.6 and 0.7 a medium effect size, and 0.8 or greater is a large effect size (Rice & Harris, 2005). We used permutation accuracy importance to define relative variable importance (Strobl, Malley, & Tutz, 2009) with the cforest package in the Party Package. Variables with negative, zero, or small positive values (left of the dotted line in Figures 4-6 to 4-8) are not important predictors of cognitive resilience to low mobility. Variables beyond this range (right of the dotted line in Figures 4-6 to 4-8) are informative and interpreted with a ranking of relative importance (McDermott et al., 2017; Strobl, Hothron, & Zeileis, 2009).

Results

Foundational Analyses

In the foundational analysis, we calculated a mobility growth model over a 40-year period. The latent growth model for mobility (higher score = better performance) indicated that individuals varied in the level of mobility, exhibited a significant decrease in mobility scores (M = -0.367, $p > 0.001$), and showed variable patterns of decline (b = -0.061, $p > 0.001$; see Figure 4-1, and Table 4-3 for comparative fit indices). This growth model was used in the subsequent analysis for RG1.

RG1: LCGA for Mobility Classes

The analysis indicated that a two-class model provided the best solution when compared with the one-class or the three-class models (AIC = 6832.37, BIC = 6867.92, -2LL = 6816.37; entropy = 0.81; see Table 4-4 for comparative fit indices). The high mobility class was characterized by higher baseline levels of mobility performance and stable or slightly declining

mobility scores over time (*n* = 504 [80%], intercept = 0.19, 95% CI [-0.04, 0.42], slope = - 0.09 95% CI [-0.11, -0.07]). The low mobility class was characterized by lower baseline levels of mobility performance and a more steeply declining mobility trajectory (*n* = 125 [20%], intercept = -2.34, 95% CI [-2.97, -1.71], slope -0.14, 95% CI [-0.17, -0.11]; see Figure 4-2).

RG2: Cognitive Resilience to Low Mobility

Memory. The memory LCGA identified a two-class memory model as the best-fitting solution (AIC = 1428.12, BIC = 1450.56, -2LL = -1412.14; entropy = 0.86; see Table 4-5 for comparative model fit indices). The higher performing subclass (resilient to low mobility) was characterized by higher baseline levels of memory performance and stable or slightly declining memory scores over time (*n* = 71 [57%], intercept = 1.94, 95% CI [1.62, 2.26], slope = -0.07, 95% CI [-0.11, -0.03]). The lower performing subclass (non-resilient to low mobility) characterized by lower baseline levels of memory performance and a more steeply declining memory trajectory (*n* = 54 [43%], intercept = -4.25, 95% CI [-4.62, -3.88], slope -0.18, 95% CI [-0.23, -0.13]; see Figure 4-3).

Speed. The speed LCGA results identified that a three-class speed model had the lowest comparative fit indices and a very good entropy value, however, the proportion for the lowest-performing subclass fell below 10% of the sample, (0.07%, *n* = 9), so the three-class model was not considered further. Therefore, the two-class model was used (AIC = 1909.89, BIC = 1932.32, -2LL = 1893.90; entropy = 0.88; see Table 4-6 for model fit indices). The higher performing subclass (resilient to low mobility) was characterized by higher baseline levels of speed performance and stable or slightly declining speed scores over time (*n* = 91 [73%], intercept = 2.98, 95% CI [2.16, 3.80], slope = -0.21, 95% CI [-0.30, -0.12]). The lower performing subclass (non-resilient to low mobility) characterized by lower baseline levels of

speed performance and a more steeply declining speed trajectory (n = 34 [27%], intercept = -11.78, 95% CI [-12.91, -10.65], slope -0.25, 95% CI [-0.8, -0.12]; see Figure 4-4).

EF. The EF LCGA identified that a two-class EF model fit the data better than the one-class or the three-class models (AIC = 645.67, BIC = 668.11, -2LL = -629.68; entropy = 0.95; see Table 4-7 for comparative model fit indices). The higher performing subclass (resilient to low mobility) was characterized by higher baseline levels of EF performance and stable or slightly declining EF scores over time (n = 110 [88%], intercept = 0.06, 95% CI [-0.05, 0.17], slope = -0.04, 95% CI [-0.05, -0.03]). The lower performing subclass (non-resilient to low mobility) characterized by lower baseline levels of EF performance and a more steeply declining EF trajectory (n = 15 [12%], intercept = -1.94, 95% CI [-2.16, -1.72], slope -0.08, 95% CI [-0.10, -0.06]; see Figure 4-5).

RG3: Predictors of Cognitive Resilience to Low Mobility

RFA was used to compute the relative predictive importance of 21 factors discriminating resilient to low mobility from non-resilient to low mobility (separately) across each of the three cognitive domains. These 21 predictors came from four domains: demographic (i.e., age, sex, education, marital status, living status, pet ownership), health (i.e., anti-inflammatory medication, peak flow, grip strength, PP, BMI, depressive symptoms, diabetes, subjective health), genetic (i.e., *APOE* and *BDNF* genetic risk status), and lifestyle (i.e., cognitive activity, social activity, physical activity, volunteer activity, alcohol use). Current smoking status (smoker or non-smoker) was originally included but was excluded from the final list due to insufficient participant rates (n = 4).

Memory Resilience to Low Mobility. Seven predictors distinguished the resilient subclass from the non-resilient subclass. Memory resilience to low mobility was predicted (in order of

relative importance) by higher physical activity, higher education, lower depressive symptoms, *APOE* genetic non-risk status, higher cognitive activity, lower alcohol use, and higher peak flow. Model classification performance indicated moderate discrimination (C = 0.63, 95% CI [0.53 – 0.73], mtry = 5, ntree = 5000). Figure 4-6 shows the predictors in order of relative importance. The predictors to the right of the vertical line have the best permutation accuracy.

Speed Resilience to Low Mobility. As can be seen in Figure 4-7, five predictors distinguished speed resilience to low mobility from non-resilience. Speed resilience to low mobility was predicted (in order of relative importance) by higher subjective health, higher peak flow, higher social activity, higher education, and younger age. Model classification performance indicated moderate discrimination (C = 0.65, 95% CI [0.54 – 0.76], mtry = 5, ntree = 5000).

EF Resilience to Low Mobility. As can be seen in Figure 4-8, five predictors distinguished the resilient subclass from the non-resilient subclass. EF resilience to low mobility was predicted (in order of relative importance) by high cognitive activity, younger age, high grip strength, higher volunteer activity, and higher social activity. Model classification performance indicated moderate discrimination (C = 0.69, 95% CI [0.54 – 0.84], mtry = 5, ntree = 5000).

Generalizability of Predictors of Resilience Across Cognitive Domains. While there were no predictors common to all three cognitive domains, there were predictors common to two of three domains of cognition (see Table 4-8). Specifically, younger age and high social activity were predictors of both EF and speed resilience to low mobility. High education and higher peak flow were predictive of both memory and speed resilience to low mobility. Additionally, high cognitive activity was a predictor of both memory resilience and EF resilience to low mobility.

Discussion

The overall aim of this chapter was to establish and define cognitive resilience to low mobility and examine factors that are predictive of resilience. To address this aim, we examined three research goals by applying a series of data-driven analytics to longitudinal trajectory distributions. First, we identified distinct, separable classes of mobility trajectories for non-demented older adults. Second, we examined cognitive resilience to low mobility across three domains of cognition (i.e., memory, speed, and EF). Cognitive resilience to low mobility was empirically defined as a high level of cognitive performance and stability or slight decline despite low mobility levels. Third, we examined multifactorial determinants of resilience, identifying factors uniquely contributing to resilience to low mobility, separately across three cognitive domains.

RG1: LCGA for Mobility Classes

Utilizing the full distribution of mobility trajectories across a 40-year band of aging, we empirically established two separate and distinct classes of level and performance. These classes were calculated based on an algorithm considering individualized mobility level and slope data. The high performing mobility class was characterized by high mobility level and slightly declining mobility over time. The low mobility class was characterized by low mobility level and rapidly declining mobility over time. We note that our low mobility class (19.8%) is relatively consistent with of the overall occurrence of mobility disability (20.6%) in a community-dwelling, non-demented older population (Statistics Canada, 2016).

A previous longitudinal study by White and colleagues (2013) characterized three trajectories of gait speed (i.e., fast decline, moderate decline, and slow decline) in 2364 older adults aged 70 – 79. Their results indicated that 22% of their sample had fast gait speed decline,

which was characterized by a slower gait speed and a steep decline in gait speed over eight years. Although we have a wider age range in our sample and include measures of balance in our mobility measure, the proportion of older adults in the 'fast decline' group is similar to our class of low mobility. Recently, a study by Ferrucci and colleagues (2016) discussed the vast heterogeneity in the trajectory of mobility loss for older adults. They proposed a hypothetical representation of individualized mobility trajectories and a grand mean, depicting the individual versus population trend in mobility from age 20 to 100. Additionally, they identified a critical inflection point in mobility decline that occurs around 70 years of age for the population yet noted that individualized trends may show these critical declines at a varied rate. Notably, our novel results empirically establish the vast variability in mobility level and change in a non-demented older population aged 55 – 95. Furthermore, we have characterized two classes within the overall mobility distribution which conceptualizes two differentially aging phenotypes. For the subsequent analyses, we used the low mobility class to characterize cognitive resilience and non-resilience.

RG2: Cognitive Resilience to Low Mobility

For the second research goal, the class of individuals with low mobility was used to examine cognitive resilience and non-resilience across three cognitive domains, memory, speed, and EF. These resilient and non-resilient trajectories were differentiated by an algorithm considering individualized level and slope data (McDermott et al., 2017; McFall et al., 2019). Notably, the LCGA revealed that cognitive trajectories in a sample of older adults with low mobility could be classified into two separate, distinct, neighboring phenotypes (i.e., higher cognitive performance and less decline, and lower cognitive performance and steeper decline trajectories). The subclass with higher cognitive performance was classified as resilient to low

mobility and the subclass with lower cognitive performance was classified as non-resilient to low mobility. Notably, a recent longitudinal study by Gonzales and colleagues (2020) identified joint trajectories of cognitive performance (measured by MMSE) and gait speed in older adults aged 65 – 74. Their results established three latent classes: (a) relatively stable cognition and gait (labelled stable cognition and gait), (b) deteriorating cognition and gait (labelled cognitive and physical vulnerability), and (c) stable cognition and deteriorating gait (labelled physical vulnerability). While their research goal was to identify joint trajectories of cognition and gait speed changes, considered with the present research, their physical vulnerability class may represent a class of older adults cognitively resilient to deteriorating gait speed. Future research could examine these subclasses of joint trajectories to identify similarities and differences when compared with the phenomenon of cognitive resilience.

Of note, our results revealed that the number of cognitively resilient individuals varied within each cognitive domain (i.e., memory resilience $n = 71$; speed resilience $n = 91$; EF resilience $n = 110$). Upon further examination, 14% ($n = 18$) were considered resilient in one of three domains, 30% ($n = 38$) were resilient in two of three domains, and 49% ($n = 61$) were resilient in all three domains. Regarding the non-resilient proportions, 7% ($n = 9$) of the low mobility sample were considered non-resilient across all three cognitive domains, 21% ($n = 20$) were non-resilient in two of three domains, and 36% ($n = 34$) were non-resilient in one of three domains. These results indicate that while resiliency is possible across three cognitive domains, it may be largely domain-specific and best measured using multiple domains. Additionally, this is one of the first studies that consider: (a) cognitive resilience across three age-sensitive domains of cognition, and (b) resilience in the lens of low mobility.

RG3: Predictors of Cognitive Resilience to Low Mobility

Overall, for the third research goal, results indicated a number of factors from four broad domains (i.e., demographic, lifestyle, health, and genetic) predicted resilient status differentially for three cognitive domains. While relevant predictors were not common across all three domains of cognition, particular predictors were similar across two of the three cognitive domains. Specifically, younger age and high social activity were common predictors of speed and EF resilience, high education and high peak flow were common to memory and speed resilience, and high cognitive activity was common to memory and EF resilience. This interesting result signifies the vast network of factors differentially influencing cognitive performance in older adults. For example, while almost 50% of individuals were cognitively resilient in all three domains of cognitive performance, most of the factors that contribute to domain-specific resilience were distinct and disparate. Unique predictors of memory resilience to low mobility included alcohol consumption, high physical activity, no depressive symptoms, and *APOE* non-risk genetic status. Subjective health was a distinctive factor differentiating speed resilience from non-resilience to low mobility. High volunteer activity and high grip strength were also distinctive to EF resilience.

Recently, Gonzales and colleagues (2020) examined the predictors contributing to joint gait and cognition trajectory differences. Their results indicated that membership in the class of low mobility and high cognitive performance (termed physical vulnerability class) was predicted by female sex and BMI. Neither factor was a predictor of cognitive resilience in the present research. Notably, they used MMSE as a global measure of cognitive function, and therefore differential predictors could be seen when examining domain-specific factors as our results

indicate. Further research in this area is necessary to establish the generalizability of our results to other older adult populations.

In the demographic domain, younger age and high education were identified as predictors of cognitive resilience in differential domain-specific patterns. It is well established that age-related cognitive declines occur outside of any neurodegenerative process, and advancing age is one of the three greatest risk factors for AD (Deary et al., 2009; Reidel, Thomspon, & Brinton, 2016; Salthouse, 2009). Additionally, education has been identified as a fundamental protective factor for cognitive health and has been positively associated with baseline cognition and delayed onset of decline (Clouston et al., 2020; Zahodne & Zajacova, 2020). This effect is thought to be a result of increased cognitive reserve (Schneeweis, Skirbekk, & Winter-Ebmer, 2014; Stern, 2012). In recent research, younger age and high education were identified as genetically robust predictors of memory resilience (McDermott et al., 2017). In contrast, while higher education was a robust predictive factor, older age was found to be a predictor of global cognitive resilience to *APOE* genetic risk for white but not black older adults. With this interesting contrast in age results, future research could examine resilience as stratified by age groups to identify potentially differential factors associated with domain-specific cognitive resilience (see McFall et al., 2019 for an example of this analyses).

In the lifestyle domain, predictors of cognitive resilience to low mobility include alcohol use, high cognitive activity, high social activity, high physical activity, and high volunteer activity. These results are consistent with recent research on memory resilience to AD genetic risk. Specifically, McDermott and colleagues (2017) identified that cognitive, physical, social, and volunteer activity predicted resilient status to AD genetic risk. Notably, the cognitively beneficial effects of an engaged lifestyle have been extensively supported in the literature

(Anstey et al., 2014; Borgeest et al., 2020; Dause & Kirby, 2019; Etnier, Drollette, & Slutsky, 2019; Kivipelto, Mangialasche, & Ngandu, 2018). The beneficial brain effects of a physically and cognitively engaged lifestyle are well documented and likely supported through neural plasticity, neurogenesis, synaptogenesis, angiogenesis, increased neural connectivity, reduced cellular atrophy, and increased cognitive reserve (Chapman, Spence, Aslan, & Keebler, 2017; Dause & Kirby, 2019; Lista & Sorrentino, 2010). Social engagement and volunteer activity are largely thought to have their effect through the relationship with cognitive and physical activity, increased social support, and more positive health behaviors (Brown, Robitaille, Zelinski, Dixon, & Piccinin, 2016; Dause & Kirby, 2019; Watt et al., 2014). Regarding alcohol, some patterns of alcohol use have been associated with cognitive benefits in older adults. Specifically, low and moderate alcohol consumption has been associated with beneficial effects, while heavy drinking has been linked to lower cognitive scores, executive impairments, brain atrophy, and a higher risk of dementia (Koch, Fitzpatrick, & Rapp, 2019; Rehm, Hasan, Black, Shield, & Schwarzinger, 2019; Topiwala, & Ebmeier, 2017).

In the genetic domain, our results indicated that *APOE* non-risk was associated with memory resilience to low mobility. This is the first known study on cognitive resilience that included genetic factors as predictors. Other recent studies on this novel concept included *APOE* genetic risk status as the main variable of interest (Kaup et al., 2015; McDermott et al., 2017). Notably, memory deficits are the cardinal marker of AD, and *APOE ε4* is the main genetic risk factor for sporadic AD. Recent evidence suggests that some of the cognitive deficits seen for *APOE* risk carriers result from developing AD neuropathology (O'Donoghue, Murphy, Zamboni, Nobre, & Mackay, 2018). Therefore, it is possible that *APOE* genetic risk carriers are

more susceptible to the effect of low mobility on memory, lending to the contribution of non-risk status to resilience.

In the health domain, predictors of cognitive resilience to low mobility included lack of depressive symptoms, higher peak flow, higher subjective health rating, and lower PP. We note that these predictors were domain-specific, with only higher peak flow common to memory and EF resilience. Comparably, McDermott and colleagues (2017) identified that these four health factors differentiated memory resilient from non-resilient classes. Depressive symptoms in late-life have been linked to lower cognitive function, faster cognitive decline, and a higher risk for dementia (Donovan et al., 2017; Singh-Manoux, Dugravot, & Fournier, 2017; Wei et al., 2019). Peak expiratory flow is a measure of pulmonary function that has been associated with both cognitive performance and walking speed in older adults (Emery, Finkel, & Pedersen, 2012; Ferreira, Tanaka, Santos-Galduroz, & Galduroz, 2015; Singh-Manoux et al., 2010; Trevisan et al., 2020). This relationship is thought to be due to reduced brain oxygenation, hypoxia, reduced neurotransmitter function, and increased inflammatory processes (Emery et al., 2012). Higher ratings of subjective health were associated with speed resilience to mobility limitation. There is a paucity of recent research on subjective health and cognitive performance, however, one older study indicated that self-reported health was associated with processing speed (Van Boxtel, Langerak, Houx, & Jolles, 1996). This is interesting, as our results indicated subjective health was a predictor of speed resilience. More research is needed in this area to examine this effect. Additionally, PP, a proxy measure of arterial stiffness, has been associated with EF performance and change in an older non-demented population (Caballero et al., 2020; McFall et al., 2013; McFall et al., 2015). Arterial stiffness is known to be a sensitive predictor of cognitive

impairment, mechanistically related through damages to the cerebral microcirculation (Li, Lyu, Ren, An, & Dong, 2017).

Taken together, RFA indicated that multiple predictors from four broad domains discriminate cognitive resilience from non-resilience to low mobility. We also note that several of these predictive factors are modifiable (i.e., alcohol use, high cognitive, physical, social, and volunteer activity, depressive symptoms, peak expiratory flow, and PP), which may lead to promising intervention targets. Conceptually, these results suggest that older adults may be able to develop cognitive resilience in spite of physical health adversities. We also note that some factors did not predict cognitive resilience to low mobility, contrary to what we had expected. Specifically, it was expected that sex and *APOE* non-risk would differentiate between EF resilient and non-resilient classes. In previous VLS research, it was found that males with low mobility levels had faster EF decline than females with low mobility levels (Thibeau, McFall et al., 2019). Moreover, *APOE* risk has also been associated with poor mobility performance and EF performance and change (Melzer et al., 2005; Sapkota, Bäckman & Dixon, 2017). Therefore, we expected that female sex would support cognitive resilience to low mobility, and that *APOE* non-risk would be a predictor of EF resilience but this expectation was not observed in the results of the present chapter. Notably, our results suggest there were distinct, domain-specific predictors of resilience, which lend evidence to the multifactorial model of cognitive aging.

Precision medicine is a newly emerging concept that refers to individualizing therapeutic approaches to disease (National Research Council, 2011). When applied to brain aging, precision medicine could be conceptualized as identifying and proactively increasing individualized resources and reducing individualized risks for cognitive decline, impairment, and dementia. To put a precision medicine model into place for cognitive aging, risk categories must be identified

in light of other genetic, demographic, lifestyle, and functional health factors (Ryan et al., 2019). Our results add to emerging evidence on the novel concept of resilience and may be applied to developing an individualized constellation of risks and resources.

Limitations and Strengths

Several limitations are noted. First, participants of the VLS were initially selected to be relatively healthy and free of neurodegenerative diseases. Additionally, these participants are predominately caucasian and possess several risk-reducing factors, such as above average education, access to health care, and are community-dwelling. Therefore, this sample may not be representative of all older adults. Notably, however, within this sample we had variable distributions within mobility and cognitive performance, representative of the range of variability within non-demented community dwelling western populations. Second, the class of individuals with low mobility comprised a relatively small sub-sample (n = 125) from which to infer cognitive resilience. A larger sample of individuals with low mobility may be more informative however, this class (20%) is representative of the overall occurrence of mobility disability (between 14 and 26%) in non-demented, older community-dwelling samples (Okoro, Holllis, Cyrus, & Griffin-Blake, 2018; Satariano et al., 2016; Statistics Canada, 2016). Furthermore, we obtained meaningful estimates and results even with this smaller sample size. Specifically, the area under the Reciever Operating Characteristic curve (C-statistic) for all three of the RFA models indicated that our pool of 21 predictors was moderately successful at discriminating resilient from non-resilient groups within this subsample of 125 individuals. Third, the EF non-resilient cell size was relatively small (e.g., 15) however, RFA is suitable for testing multiple predictors even with small sample sizes (Strobl, Hothron, & Zeileis, 2009), and we obtained a moderate AUC value (C = 0.69, equivalent to d = 0.70) (Salgado, 2018) with meaningful

predictive results. Future research could use data augmentation approaches (i.e., under sampling the larger subclass and oversampling the smaller subclass) with the EF subclass to see if there is a difference in the AUC estimates and discriminating predictors. Fourth, predictors of resilience were tested at baseline, and not against second or third data collection points. Future research could examine longitudinal predictors of resilience to test the robustness of these resilience predictors over time. Fifth, smoking was originally included in the set of predictors, however, was not used due to a low frequency of participation (n = 4). Additionally, other factors that could be related to cognitive resilience such as sleep time, nutritional status, cholesterol levels, and psychological resources, were not available in the VLS battery. Future research could include a broader constellation of predictors to assess the impact on cognitive resilience to AD risk factors.

Five main strengths of this research are noted. First, we note the use of a sizeable, well characterized sample of non-demented community-dwelling older adults tested at three waves (wave 1, n = 632). This initial sample allowed us to portray the vast heterogeneity in mobility trajectories among older adults, displayed in Figure 4-1. To our knowledge, this is the first study to examinevariability in mobility trajectories and include model-based trajectory subclass analysis. This trajectory-based subclass analysis identified novel patterns of mobility stability and mobility decline within the overall sample. Second, we note the focus on cognitive resilience to low mobility. We classified a novel concept, cognitive resilience, by using the individualized level and slope trajectories across multi-indicator latent variables. Notably, this classification was performed separately on three age-sensitive domains of cognitive function, namely, memory, speed, and EF. Third, we used an accelerated longitudinal design, spanning a 40-year band of aging, which allowed us a robust examination of mobility and cognitive trajectories in

older adults. Fourth, age was used both as the metric of change, which enabled us to examine individualized trajectories of mobility and cognitive function over a broad band of human aging, and as a predictor of cognitive resilience. Fifth, we used contemporary statistical approaches (including LCGA and RFA) to sequentially examine our research goals. These advanced data-driven modern approaches provide objective classification and high prediction accuracy within this non-demented sample of older adults (Cabellero et al., 2020; McFall et al., 2019).

In summary, we provide evidence of: (a) significant heterogeneity in level and slope of mobility trajectories for an older non-demented population, (b) data-driven identification of subclasses within this broad mobility distribution, and (c) identification of resilient and non-resilient subclasses of cognitive performance. Notably, the greater number of resilient compared with non-resilient individuals across all three cognitive domains supports that resilience may be ubiquitous (Staudinger & Greve, 2015). Therefore, developing resilience is a very promising and feasible target for older adults, despite the presence of AD risk factors. In that line, our results also indicate that multiple predictors from four broad domains (i.e., health, genetic, demographic, and lifestyle) differentiate between cognitively resilient and non-resilient individuals. Taken together, the promotion of cognitive resilience to low mobility may occur through developing a constellation of resources to offset dementia risk. Notably, better understanding of the drivers of resilience offers the opportunity to develop more effective interventions targeted at improving the resources needed to overcome risks and vulnerabilities.

Table 4-1

Baseline Descriptive Statistics for Low Mobility Class (n = 125)

	Low Mobility Class	Memory Resilience	Memory Non-Resilience	Speed Resilience	Speed Non-resilience	EF Resilience	EF Non-resilience
	n = 125	n = 73	n = 52	*n* = 91	*n* = 34	*n* = 108	*n* = 17
Age (years)	71.31 (8.04)	70.50 (7.50)	71.88 (8.61)	70.03 (7.62)	73.95 (8.38)	70.41 (7.36)	76.05 (10.35)
Sex (% female)	77.90	68.6	55.80	61.8	66.7	61.30	76.50
Education (years)	15.1 (3.13)	15.75 (3.12)	14.27 (3.0)	15.48 (2.95)	14.15 (3.48)	15.24 (3.19)	14.24 (2.77)
Mobility Score	-0.40 (1.62)	0.23 (1.63)	-0.43 (1.51)	0.31 (1.42)	-1.0 (1.77)	0.26 (1.41)	-1.74 (1.68)
Memory Score	-0.49 (6.36)	0.18 (0.56)	-0.53 (1.05)	0.15 (0.57)	-.86 (1.10)	0.13 (0.50)	-1.76 (0.98)
EF Score	-0.15 (0.89)	2.03 (1.90)	-3.68 (2.70)	0.60 (3.15)	-3.13 (3.46)	0.12 (3.20)	-3.86 (4.30)
Speed Score	-0.90 (7.79)	2.26 (5.26)	-4.63 (8.48)	3.01 (3.96)	-10.63 (5.93)	0.67 (6.73)	-9.65 (6.87)
MMSE	28.75 (1.29)	28.96 (1.17)	28.51 (1.38)	28.85 (1.24)	28.57 (1.34)	28.90 (1.17)	27.81 (1.64)

Note. Baseline descriptive statistics for the low mobility class. Abbreviations: EF, executive function; MMSE, Mini-mental state examination score

Table 4-2

Bivariate Correlations for Predictors of Cognitive Resilience to Low Mobility

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1. Age	1																					
2. Education	-0.013	1																				
3. Sex	0.109	0.055	1																			
4. Marital Status	-0.118	0.001	**0.267****	1																		
5. Living Status	-0.064	-0.024	**0.444****	**0.354****	1																	
6. Pet Ownership	-0.024	0.025	0.015	-0.014	0.118	1																
7. Smoking	0.008	0.098	0.017	0.047	**-0.195***	-0.127	1															
8. Alcohol Use	0.133	0.126	0.055	0.064	**0.275****	0.052	-0.057	1														
9. Social Activity	-0.031	0.053	-0.080	-0.059	-0.129	-0.077	0.018	-0.133	1													
10. Cognitive Activity	**-0.255****	**0.348****	0.241**	**0.012**	**0.215***	-0.069	0.012	0.032	**0.272****	1												
11. Volunteer Activity	-0.061	0.166	-0.127	-0.034	**-0.242****	-0.037	0.092	-0.131	**0.721****	0.150	1											
12. Physical Activity	**-0.182***	0.096	0.040	-0.076	0.119	0.074	-0.164	0.018	0.062	**0.345****	0.115	1										
13. Pulse Pressure	**0.546****	-0.072	-0.059	-0.002	0.016	0.075	-0.022	0.142	-0.164	**-0.193***	-0.156	-0.160	1									
14. Body Mass Index	0.002	0.027	0.045	-0.126	-0.164	**0.217***	-0.083	-0.149	-0.041	0.029	0.045	-0.166	0.128	1								
15. Grip Strength	**-0.268****	0.023	**0.740****	**-0.180***	**0.355****	0.051	0.012	0.067	-0.114	**0.292****	-0.134	0.079	**-0.225***	0.107	1							
16. Depressive Symptoms	-0.097	-0.067	-0.110	0.043	-0.026	-0.024	-0.008	-0.060	-0.067	-0.111	-0.092	-0.173	-0.068	0.005	-0.027	1						
17. Diabetes	-0.072	-0.128	0.120	-0.016	-0.071	-0.068	-0.063	**-0.248****	-0.029	-0.022	0.066	-0.108	0.065	**0.312****	0.077	-0.026	1					
18. Subjective Health	0.094	-0.089	-0.097	-0.020	-0.158	0.037	-0.016	-0.057	-0.144	-0.173	-0.093	-0.158	**0.230***	0.132	-0.141	-0.008	**0.184***	1				
19. Antiinflammatory Medication	-0.043	0.011	-0.072	0.138	-0.145	-0.066	0.050	0.131	-0.096	-0.081	-0.099	**-0.286****	0.009	0.071	-0.048	0.045	-0.028	**0.293****	1			
20. Peak Flow	**-0.184***	0.160	**0.620****	**-0.227***	**0.309****	-0.011	-0.106	0.032	-0.006	**0.330****	0.000	0.159	**-0.223***	-0.021	**0.631****	0.029	0.051	-0.171	-0.082	1		
21. *APOE*	-0.120	0.104	0.122	0.020	0.104	-0.089	0.076	-0.036	0.038	0.175	0.005	0.152	-0.053	-0.017	0.124	-0.052	-0.101	-0.101	-0.147	**0.204***	1	
22. *BDNF*	-0.115	-0.099	-0.035	**0.210***	0.163	0.074	-0.039	-0.130	-0.170	-0.173	-0.156	-0.072	0.074	-0.059	0.086	0.144	0.026	0.014	-0.123	0.015	-0.052	1

Note. Correlations were calculated for entire low mobility sample (n = 125). Abbreviations: BMI, body mass index; *APOE*, Apolipprotein E; *BDNF*, brain–derived neurotrophic factor.

*Significant at $p < 0.05$, ** $p < 0.001$

Table 4-3

Goodness of Fit Indices for Mobility Growth Model

Model	-2LL	AIC	BIC	D	Δdf	*p*
Fixed Intercept	5351.34	3533.34	5363.92			
Random Intercept	4808.28	4814.27	4827.14	555.64	1	< 0.001
Random intercept, fixed slope	4376.88	4384.88	4402.04	431.40	1	< 0.001
Random intercept, random slope*	**4198.15**	**4210.43**	**4235.89**	**178.73**	**2**	**< 0.001**

Note. -2LL = -2 Log likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; *D* = difference statistic (using -2LL); Δdf = change in degrees of freedom; -2LL = -2 Log likelihood

*Best fitting model

Table 4-4

Goodness of Fit Indices for One to Three-Class Mobility Latent Growth Mixture Models

Model	Class	AIC	BIC	2LL	Entropy	Probability	Proportion	n
1	1	7320.74	7342.96	-7310.74	-	1	1	629
2*	**1**	**6832.37**	**6867.92**	**-6816.37**	**0.813**	**0.973**	**0.8**	**504**
	2	**-**	**-**	**-**	**-**	**0.844**	**0.2**	**125**
3	1	6695.71	6744.59	-6673.71	0.743	0.93	0.63	396
	2	-	-	-	-	0.86	0.07	41
	3	-	-	-	-	0.781	0.31	192

Note. *Best fitting model. Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; -2LL, -2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimate model; n, sample size.

Table 4-5

Goodness of Fit Indices for One to Three-Class Memory Latent Growth Mixture Models

Model	Class	AIC	BIC	2LL	Entropy	Probability	Proportion	n
1	1	1572.91	1589.93	-1565.92	-	1	1	125
2*	**1**	**1428.12**	**1450.56**	**-1412.14**	**0.86**	**0.96**	**0.43**	**54**
	2	**-**	**-**	**-**	**-**	**0.97**	**0.57**	**71**
3	1	1369.38	1400.22	-1347.68	0.86	0.88	0.17	20
	2	-	-	-	-	0.95	0.39	47
	3	-	-	-	-	0.92	0.45	55

Note. *Best fitting model. Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; -2LL, -2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimate model; *n*, sample size.

Table 4-6

Goodness of Fit Indices for One to Three-Class Speed Latent Growth Mixture Models

Model	Class	AIC	BIC	2LL	Entropy	Probability	Proportion	n
1	1	2046.23	2060.25	2036.23	-	1	1	125
2*	**1**	**1909.89**	**1932.32**	**1893.9**	**0.88**	**0.951**	**0.27**	**34**
	2	**-**	**-**	**-**	**-**	**0.974**	**0.73**	**91**
3	1	1807.92	1838.76	1785.92	0.89	0.982	0.07	9
	2	-	-	-	-	0.922	0.4	50
	3	-	-	-	-	0.966	0.52	65

Note. *Best fitting model. Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; -2LL, -2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimate model; *n*, sample size.

Table 4-7

Goodness of Fit Indices for One to Three-Class EF Latent Growth Mixture Models

Model	Class	AIC	BIC	2LL	Entropy	Probability	Proportion	n
1	1	781.73	795.75	771.74	-	1	1	125
2*	**1**	**645.67**	**668.11**	**629.68**	**0.95**	**0.963**	**0.12**	**15**
	2	**-**	**-**	**-**	**-**	**0.989**	**0.88**	**110**
3	1	583.63	614.48	561.64	0.86	0.95	0.75	94
	2	-	-	-	-	0.924	0.21	26
	3	-	-	-	-	0.985	0.03	5

Note. *Best fitting model. Abbreviations: EF, Executive Function; AIC, Akaike information criteria; BIC, Bayesian information criteria; -2LL, -2 log likelihood; Probability, probability of latent class membership; Proportion, proportion for the latent classes based on estimate model; *n*, sample size.

Table 4-8

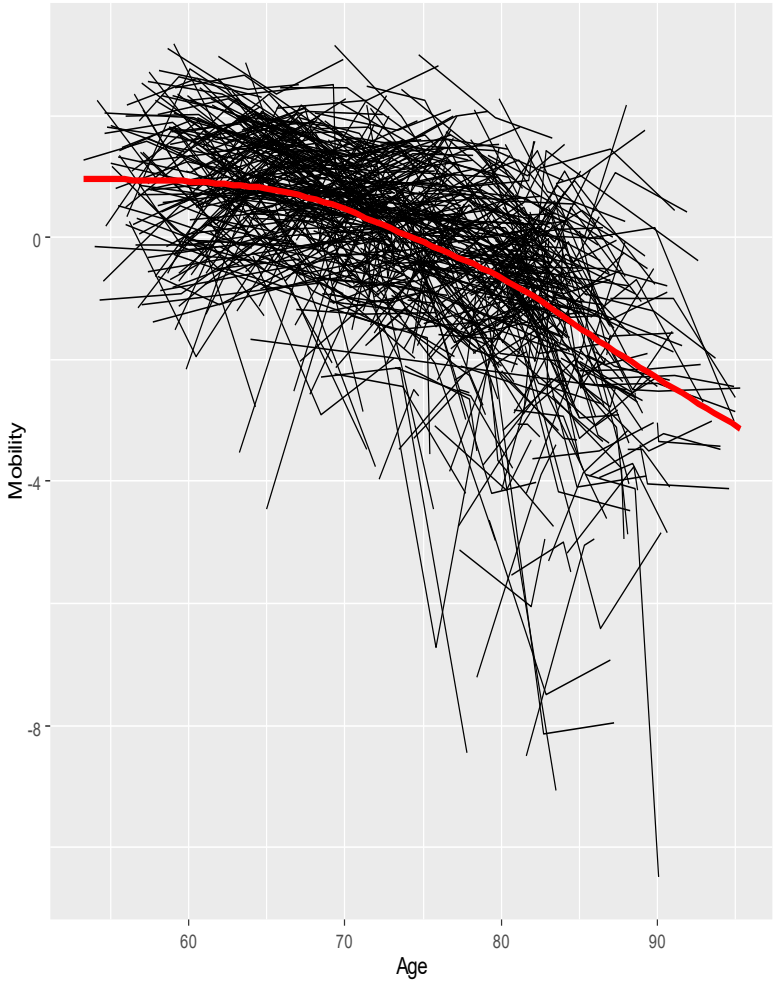
Generalizability of Predictors of Resilience to Low Mobility Across Cognitive Domains

	Memory	Speed	EF
Age		X	X
Education	X	X	
Sex			
Marital Status			
Living Status			
Pet Ownership			
Alcohol Use	X		
Cognitive Activity	X		X
Social Activity		X	X
Volunteer Activity			X
Physical Activity	X		
Diabetes			
Depressive Symptoms	X		
Peak Flow	X	X	
Subjective Health		X	
Anti-inflammatory Medication			
Grip Strength			X
Pulse Pressure			
BMI			
APOE	X		
BDNF			

Note. Abbreviations: BMI, body mass index; *APOE*, Apolipprotein E; *BDNF*, brain–derived neurotrophic factor

Figure 4-1

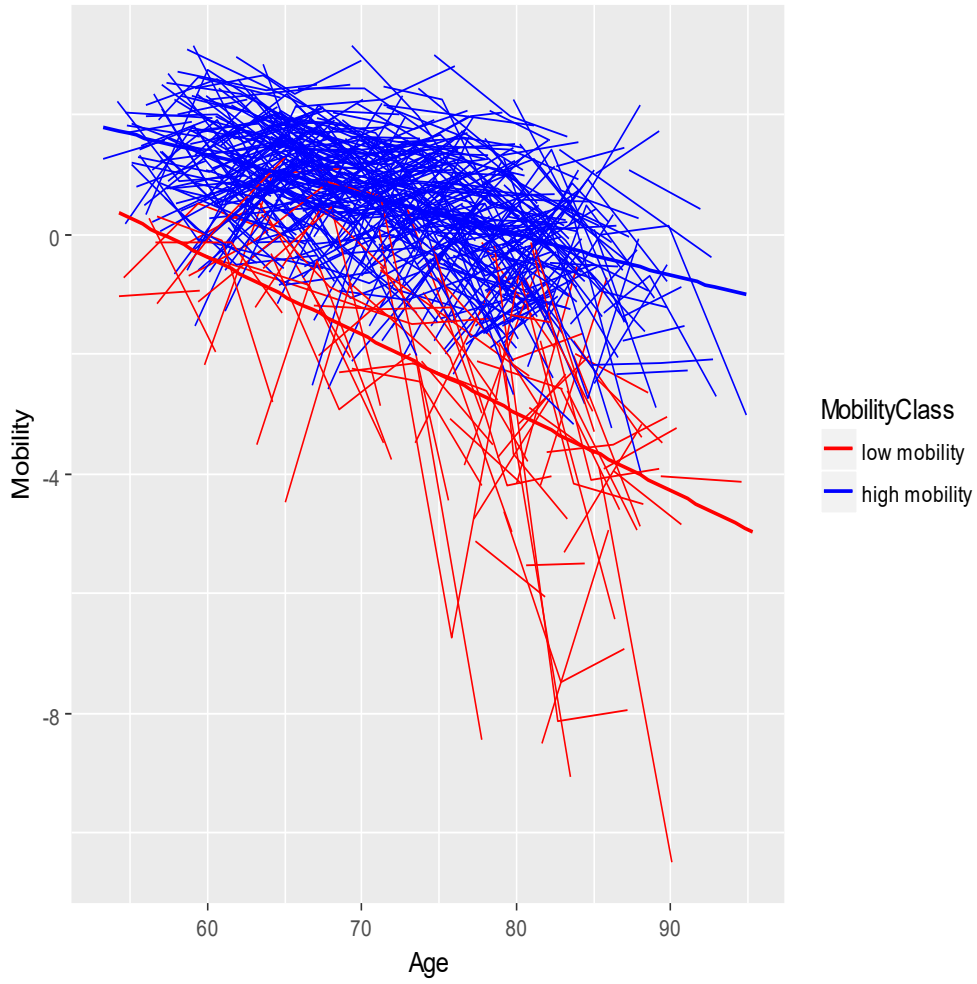
Mobility Trajectories Across a 40-Year Band of Aging



Note. Individualized mobility trajectories. The red line is the group mean trajectory line (final growth model random intercept, random slope; D = 178.73, Δdf = 2, $p < 0.001$).

Figure 4-2

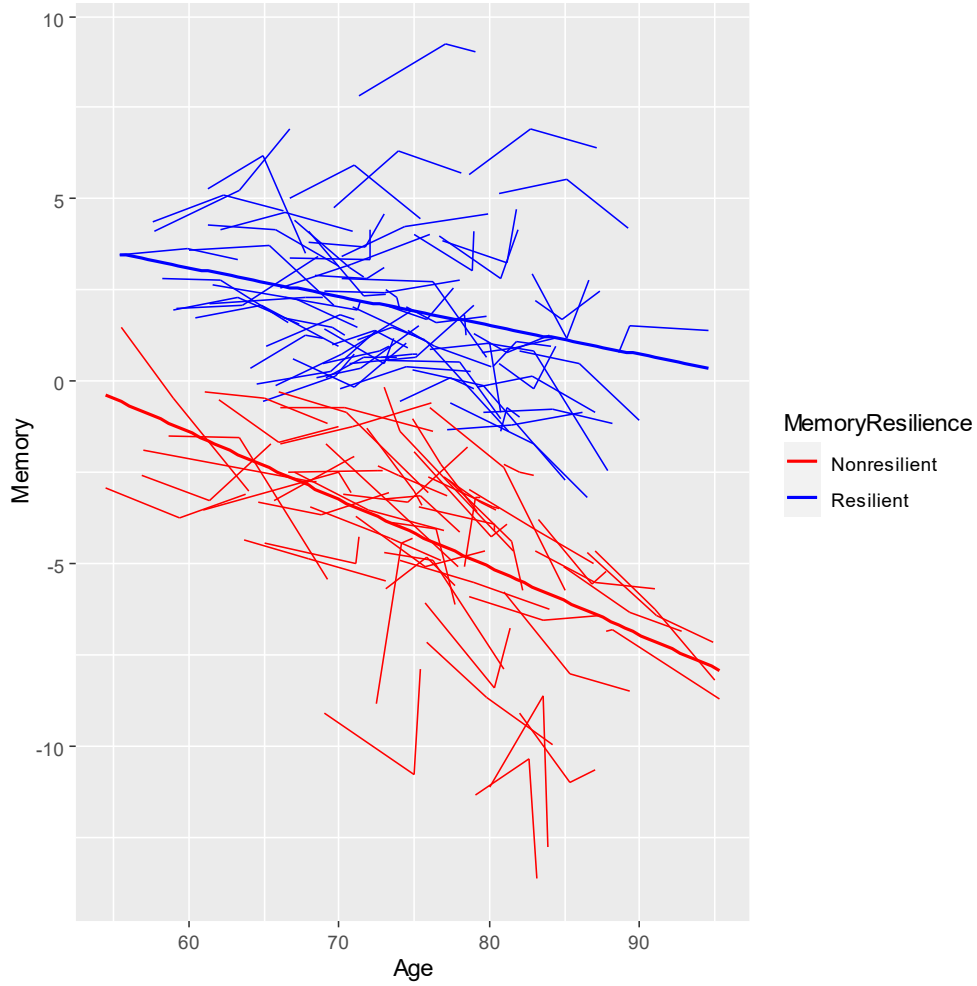
Mobility Trajectories Differentiated into a 2-Class Model



Note. Individualized mobility trajectories differentiated into two classes (i.e., high mobility n = 504, low mobility n = 125) based on level and slope with latent class growth analysis. Blue lines represent high (better) mobility, red lines represent low mobility (worse). Additionally, overall mean trajectory lines are displayed in the same colour.

Figure 4-3

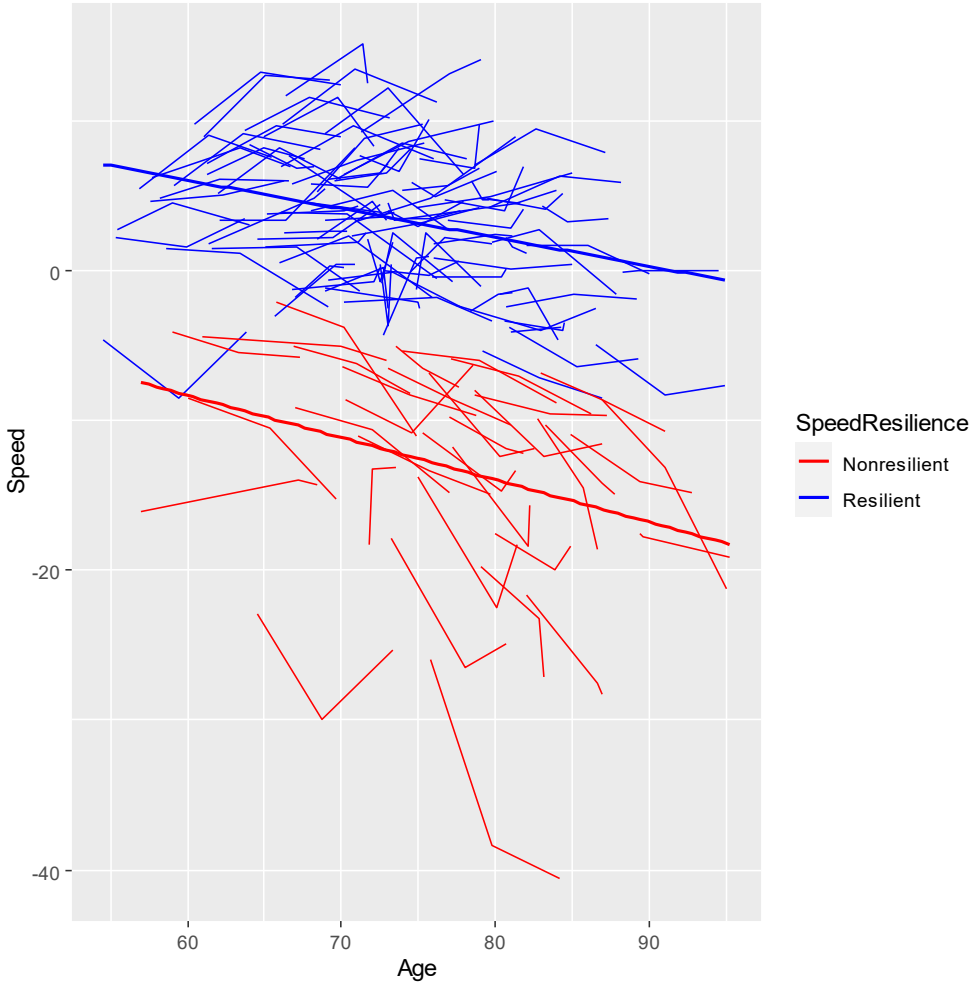
Memory Trajectories Within the Low Mobility Class



Note. Memory trajectories differentiated into a 2-class model based on level and slope of memory with latent class growth analysis. Blue lines represent higher performing (i.e., memory resilience to low mobility, $n = 71$), while red lines represent lower performance (i.e., non-resilience to low mobility, $n = 54$). Additionally, overall mean trajectory lines are displayed in the same colour.

Figure 4-4

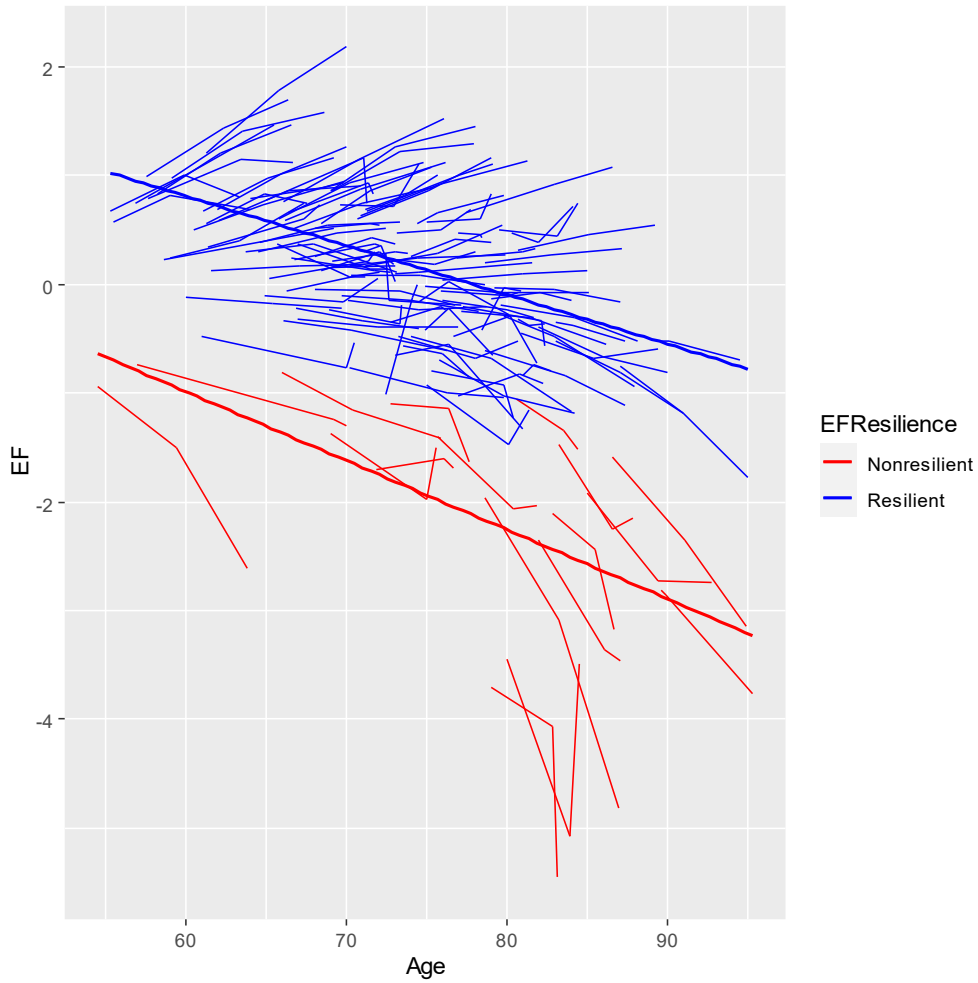
Speed Trajectories Within the Low Mobility Class



Note. Speed trajectories differentiated into a 2-class model based on speed performance and change. Blue lines represent higher performance (i.e., speed resilience to low mobility, $n = 91$), while red lines indicate lower performance (i.e., non-resilience to low mobility, $n = 34$). Additionally, overall mean trajectory lines are displayed in the same colour.

Figure 4-5

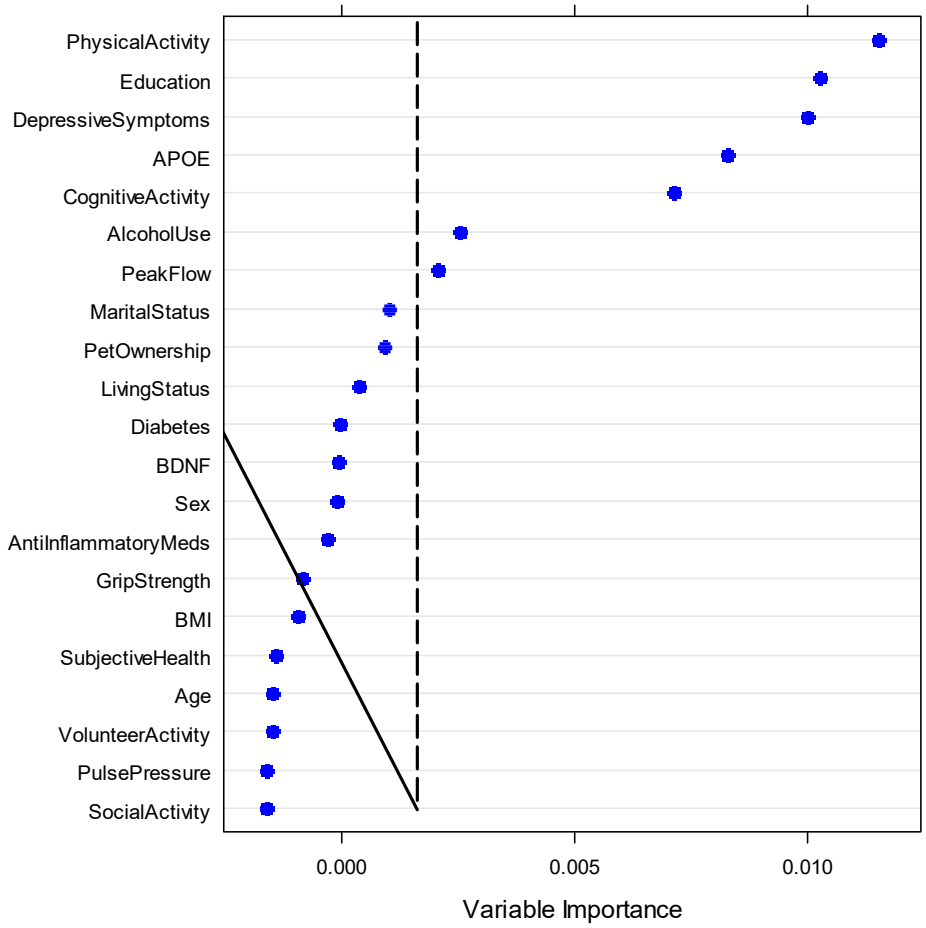
Executive Function (EF) Trajectories Within the Low Mobility Class



Note. EF trajectories differentiated into a 2-class model based on level and slope. Blue lines represent higher performance (i.e., EF resilience to low mobility, n = 110), while red lines indicate lower performance (i.e., non-resilient to low mobility, n = 15). Additionally, overall mean trajectory lines are displayed in the same colour.

Figure 4-6

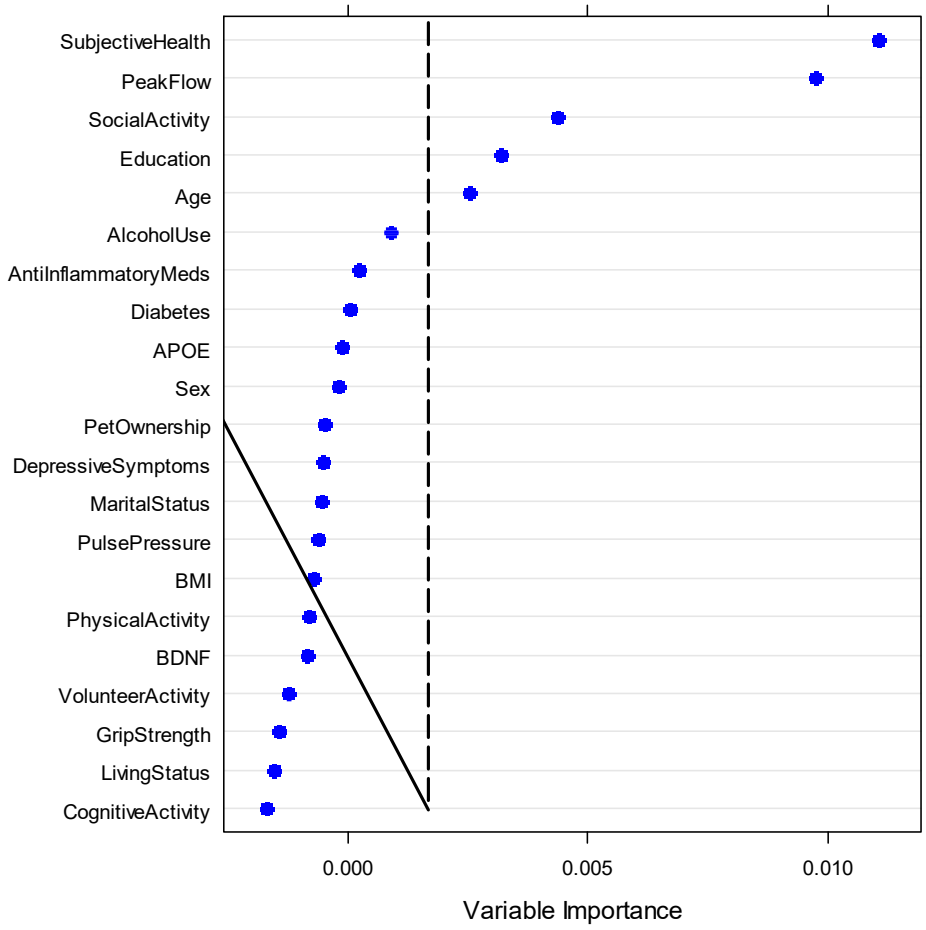
Relative Importance of Predictors of Memory Resilience to Low Mobility



Note. Predictors of resilience to low mobility versus non-resilience to low mobility. Dotted line represents cut-off values for variable importance. Variable importance was calculated based on the mean decrease in accuracy; (C = 0.63; 95% CI [0.53 – 0.73]; *n* = 125). Predictors to the right of the vertical line have the best permutation accuracy importance. Abbreviations: BMI, body mass index; *BDNF*, brain–derived neurotrophic factor.

Figure 4-7

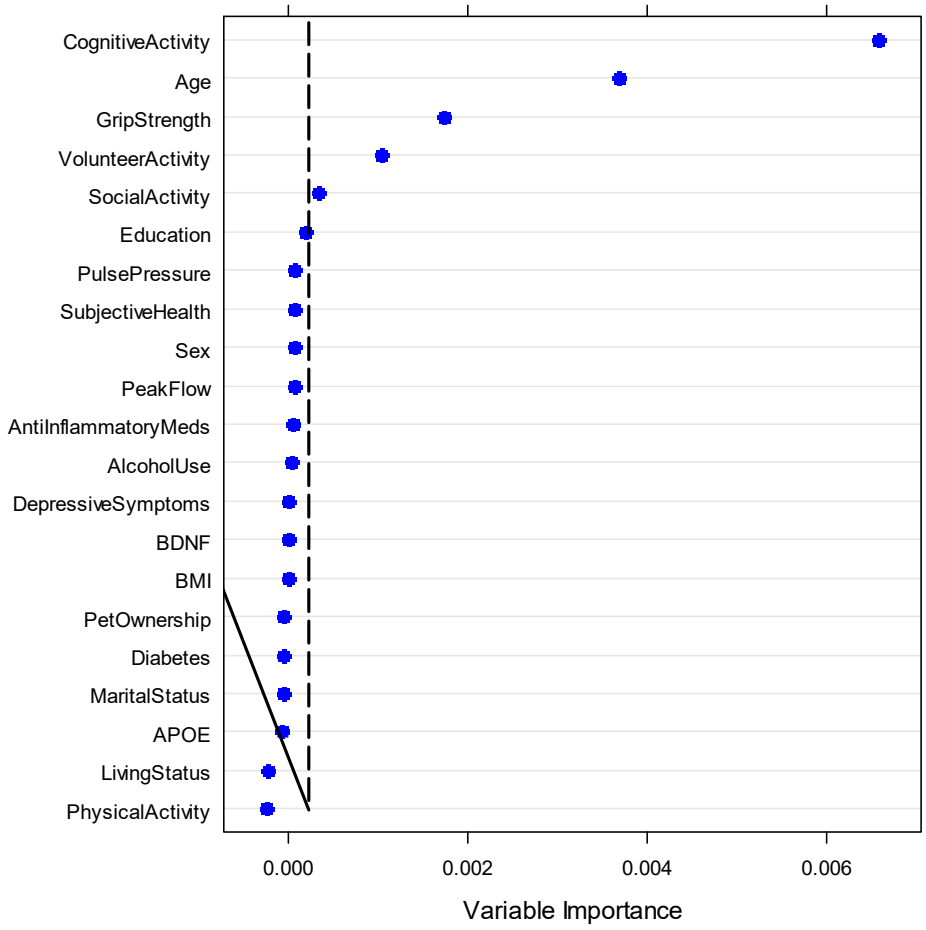
Relative Importance of Predictors of Speed Resilience to Low Mobility



Note. Predictors of speed resilience versus non-resilience to low mobility. Dotted line represents cut-off values for variable importance. Variable importance was calculated based on the mean decrease in accuracy, (C = 0.65; 95% CI [0.54 – 0.76]; *n* = 125). Predictors to the right of the vertical line have the best permutation accuracy importance. Abbreviations: BMI, body mass index; *BDNF*, brain–derived neurotrophic factor; *APOE*, Apolipoprotein.

Figure 4-8

Relative Importance of Predictors of EF Resilience to Low Mobility



Note. Predictors of EF resilience versus non-resilience to low mobility. Dotted line represents cut-off values for variable importance. Variable importance was calculated based on the mean decrease in accuracy, (C = 0.69; 95% CI [0.54 – 0.84]; *n* = 125). Predictors to the right of the vertical line have the best permutation accuracy importance. Abbreviations: BMI, body mass index; *BDNF*, brain–derived neurotrophic factor.

Chapter Five: General Discussion

The overall goal of the three longitudinal, programmatic studies within this dissertation was to examine the emerging concept of cognitive resilience despite the presence of either of two forms of detectable physical health adversity in a non-demented, community-dwelling, older population. Framed by a developmental lifespan perspective, and conceptually guided by the theories of individual differences (Hertzog, 2008), resilient brain aging (Park & Bischof, 2013), and the cognitive health and environment life course model (Anstey, 2014), this research utilized a salutogenic approach to examining cognitive resilience relative to two major predictors of cognitive decline, impairment, and dementia. We achieved this overall aim in a series of sequential analyses, across three longitudinal studies. As the results and details of each study are explicitly discussed in Chapters Two, Three, and Four, this general discussion will give a broad overview of the main results, integrated and compared across studies. Specifically, considering and integrating the commonalities across the chapters, the results of the research are identified in four main features. First, we established the influence of frailty on cognitive performance across three domains, as moderated by sex and *APOE* genetic risk status. Second, we established variability in the level and slope of individualized frailty and mobility trajectories and identified homogeneous classes within the overall heterogeneous frailty and mobility distributions. Third, we examined the classes of individuals with frailty and low mobility with regards to cognitive performance, establishing cognitive resilience to two physical health adversities. Specifically, cognitive resilience was established if the individual had relatively high cognitive performance and stable or slight change over time, despite the presence of a significant physical health adversity. Fourth, we identified common and distinct predictors distinguishing cognitively

resilient from non-resilient subclasses. These overall results are discussed integratively in the ensuing paragraphs.

Frailty Influence on Cognitive Performance and Change

Frailty has been associated with adverse brain and cognitive outcomes (Rockwood et al., 2007). In Chapter Two, we aimed to examine the influence of frailty on longitudinal change in three domains of cognitive performance. We were guided by two overall orienting questions: "Does frailty performance and change influence cognitive performance and change?" and "Do these frailty-cognition relationships differ by sex or *APOE* genetic risk status?". We used structural equation modeling to investigate how frailty performance or change in frailty influenced level and change in memory, speed, and EF. With these parallel process analyses, we were able to examine longitudinal relationships between frailty and cognition and separate these effects by sex and *APOE* genetic risk status. Our results indicated that the effect of frailty may be domain-specific, and that other risk factors for AD may moderate these effects. This research was among the first to contribute information about the multifactorial influences on the frailty-cognition relationship. Once the frailty-cognition relationship was established relative to three age-sensitive domains of cognitive performance, this research also initiated the examination of frailty trajectory classification, discussed in the following section.

Frailty and Mobility Trajectory Classes

The primary orienting questions for the studies presented in Chapters Three and Four were (a) "Do older adults vary in frailty and mobility performance and change over time?" and (b) "Can we separate older adults into classes within the overall frailty and mobility trajectories?". Important results of this phase of the third and fourth chapters include empirical establishment of the vast heterogeneity in level and change frailty and mobility. Specifically,

separate analyses of frailty and mobility revealed that non-demented older adults had significant variability in initial level and rates of change. Additionally, these trajectory distributions were further analyzed into classes based on data driven LCGA utilizing individualized level and slope algorithms. Specifically, two classes were identified (separately) for frailty and mobility. First, a frail class was characterized by a higher initial level of frailty and a steep increase in frailty. Second, the non-frail class was characterized by a lower initial level of frailty and a stable or slight increase in frailty over time. For mobility, a higher mobility (better) class was characterized by higher initial mobility level and stable or slight decrease in mobility across time, while a lower mobility (worse) class was characterized by low initial mobility level and steeper decrease in mobility. Notably, of the 125 older adults with low mobility, only 16% (n = 20) were also classified as having frailty. This comparison shows that although mobility limitations contribute to the overall construct of frailty, these two physical adversities are separate and relatively unshared by this older adult group.

Previous studies have identified separable frailty and mobility classes within older adult populations using similar data-driven analytic approaches. Specifically, Stow and colleagues (2018) examined monthly frailty index scores over a one-year period in a sample of 26000 older adults over the age of 75. Using latent class growth mixture models, they idenitfied three distinct frail classes: stable, moderately increasing, and rapidly rising classes. They further noted that the rapidly rising frail class was associated with an increased risk of mortality in older adults. With regard to mobility, a longitudinal study by White and colleagues (2013) used latent class analysis to identify three classes of gait speed (i.e., fast decline, moderate decline, and slow decline) in 2364 older adults between the ages of 70 to 79. They also reported that rapidly declining gait speed was associated with an increased risk of mortality. In comparison, our sample of older

adults was comprised of adults aged 53 to 95; therefore, we offer evidence of variability in frailty and mobility trajectories across a wider age range, using a similar data-driven analytic approach. Additionally, while the aforementioned research has examined the negative consequences of frailty or low mobility (i.e., mortality), the present research takes a salutogenic approach by examining resilience, which could be conceptualized as the converse of mortality (MacLeod, Musich, Hawkins, Alsgaard, & Wicker, 2016).

Empirically Characterizing Cognitive Resilience

After discriminating the trajectory classes in Chapters Three and Four, we then empirically established cognitive resilience in the presence of one of two physical health adversities, frailty (Chapter Three) and low mobility (Chapter Four). The overall orienting question for the analyses was "Are older adults able to maintain cognitive performance over time, despite having a physical health adversity?". Therefore, using the classes of individuals with either frailty or low mobility, we applied LCGA to identify those who displayed cognitive resilience by performing at a relatively high and stable level despite the presence of one of the adversity factors. We performed these analyses separately in the trajectory distributions for the three cognitive domains. In contrast, non-resilience was operationally characterized as relatively lower and declining cognitive performance inthe presence each of these two adversities.

Notably, our results indicated that a large proportion of non-demented older adults in our study with either (a) frailty or (b) low mobility were objectively classified as cognitively resilient. For example, regarding cognitive resilience to frailty, between 55 and 69% of older adults were classified as resilient, depending on the cognitive domain. For cognitive resilience to low mobility, between 58 and 86% of older adults were classified as resilient. This evidence emphasizes the ubiquity of resilience in the context of non-demented aging. Even under

conditions such as advancing age and physical health adversities, older adults are able to maintain levels of cognitive functioning (Anstey & Dixon, in press; Staudinger & Greve, 2016).

Correspondingly, McDermott and colleagues identified that 61% (n = 110) of their sample of older adults with *APOE* ε4 genetic risk were classified as cognitively resilient, and 62% (n = 134) of their sample with *CLU* genetic risk were classified as cognitively resilient. In contrast, Kaup and colleagues (2015) termed only 28% *(*n = 187) of the *APOE* ε4 carriers as resilient. This discrepancy in the proportion of resilient older adults could be due to (a) statistical methods used to establish resilient subclasses, (b) conceptually different definitions of resilience. or (c) different samples. For example, latent class growth analyses used in the present research to establish resilience directly within the context of risk. Latent class growth modeling is a data-driven technique to identify meaningful homogeneous subpopulations within the larger heterogeneous distribution (Jung & Wickrama, 2008). Specifically, in Chapters Three and Four, higher (resilient) and lower (non-resilient) performing subclasses were established within the class of individuals with the adversity. In contrast, Kaup and colleagues (2015) used linear mixed-effects regression models to characterize global cognitive trajectories and then defined resilience by using change values which compared trajectories from the highest tertile of *APOE* risk carriers with the entire cohort. In their study, cognitive resilience was determined relative to the cognitive performance of the entire cohort (including non-risk carriers). Notably, these are two theoretically and methodologically distinct ways of conceptualizing resilience. Of importance, our definition of resilience was directed from a salutogenic perspective, which assumes that older adults are characterized by risk factors for cognitive decline yet focuses on the resources that explain maintenance of cognitive health (Antonovsky, 1996). In addition, the method we used is person-centered and data-driven; it determines resilience based on

individualized cognitive trajectories directly in the presence of the adversity. In contrast, the approach, used by Kaup and colleagues (2015), determines resilience in a group-centered manner, considering at-risk individuals resilient only if they perform at the highest level of the other older adults without the adversity risk factor. While an instructive way of characterizing superior cognitive performance despite the presence of a risk factor, it may negate or dismiss the trajectories of those who maintain their level of cognitive performance at a lower level than non-risk carriers. Yet, these individuals may indeed be cognitively resilient, as resilience may not assume superior performance, but rather stabilization within the context of risk. Taken together, as this newly emerging area grows, future research may benefit from a consensus in empirically defining and examining resilience in general (Anstey & Dixon, in press) and cognitive resilience in particular.

Predictive Profiles of Cognitive Resilience

As resilience is the product of a constellation of risk and resources which may be variable both between and within people and domains of functioning (Staudinger & Greve, 2016), in Chapters Three and Four, we also examined predictors which distinguished between cognitively resilient and non-resilient subclasses. Specifically, we aimed to answer the questions "What factors distinguish cognitively resilient from non-resilient older adults?", and "Are the factors that contribute to resilience domain-specific, or are they generalized?". To answer these questions, RFA was used to examine the predictive importance of factors previously associated with resilience, frailty, or mobility, separately across all three domains of cognition. Specifically, in Chapter Three, we examined whether 12 factors discriminated between cognitive resilience and non-resilience to frailty separately for memory, speed, and EF. These 12 factors can be grouped into three domains: demographic (i.e., age, education, sex, marital status, living status,

pet ownership); lifestyle (i.e., alcohol use, social activity, cognitive activity, and volunteer activity); and genetic (i.e., *APOE* and *BDNF* genetic risk status). In Chapter Four, we performed similar analyses with the core set of predictors combined with nine additional factors: one from the lifestyle domain (i.e., physical activity), and eight from the health domain (i.e., diabetes, depressive symptoms, peak flow, subjective health, PP, grip strength, BMI, and the use of anti-inflammatory medication). See Table 5.1 for a comparison of the predictive factors across frailty andlow mobility, in all three cognitive domains. The results from both chapters are discussed integratively here relative to the cognitive domains, namely memory, speed, and EF.

Briefly, regarding memory resilience to frailty, results indicated (in order of importance) female sex, high education, being married, alcohol use, and high cognitive activity all differentiated resilient from non-resilient older adults (Chapter Three). Additionally, memory resilience to low mobility was predicted by (in order of importance): high physical activity, high education, no depressive symptoms, *APOE* non-risk status, high cognitive activity, alcohol use, and high peak expiratory flow (Chapter Four). When comparing predictive factors between frailty and low mobility, we note that high education, high cognitive activity, and alcohol use were predictive of memory resilience to both physical health adversities. Notably, these results are consistent with recent research on memory resilience to genetic risk. Specifically, high education and high cognitive activity were robust predictors of memory resilience to genetic risk (McDermott et al., 2017). Additionally, in their research, alcohol use predicted memory resilience to *CLU* genetic risk, but only for females.

Regarding speed resilience, our results indicated only high cognitive activity was predictive of resilience to frailty (Chapter Three). In contrast, speed resilience to low mobility was predicted by high subjective health rating, high peak expiratory flow, high social activity,

high education, and younger age (Chapter Four). We did not find common predictors of speed resilience across the two physical health adversities. This suggests that speed resilience is unique to the risk factor being considered, indicating further research is necessary to elucidate this phenomenon.

With regard to EF resilience to frailty, predictors discriminating resilient from non-resilient older adults included (in order of importance): younger age, high education, and high cognitive activity (Chapter Three). For EF resilience to low mobility, predictors (in order of importance) included: high cognitive activity, younger age, high grip strength, high volunteer activity, and high social activity (Chapter Four). Common predictors to both physical health adversities included younger age and higher cognitive activity. Notably, these studies may be among the first to examine resilience across speed and EF domains of cognition. Future research could examine predictors of speed and EF resilience to other types of risk for AD, including genetic risk, and compare with the novel results in the present research.

As noted, while investigating cognitive resilience to frailty and low mobility across cognitive domains, we found similarities and differences in predictors of resilience, as discussed in the following paragraphs.

Similarities in Predictors of Resilience to Frailty and Low Mobility. Across both frailty and low mobility and all three cognitive domains (i.e., six set of predictive analyses), the most common predictor of resilience was high cognitive activity in everyday life, which discriminated resilient from non-resilient subclasses for all but speed resilience to low mobility. In addition, high education discriminated resilience from non-resilience for all but speed resilience to frailty and EF resilience to low mobility. Correspondingly, McDermott and colleagues (2017) found that high education and high cognitive activity were robust predictors of resilience to *APOE* and

CLU genetic risk for males and females. Likewise, Kaup and colleagues (2015) found that high education and a literacy level over the 9th grade were racially robust predictors of global cognitive resilience. Mechanistically, it is thought that high education and high cognitive activity are beneficial to cognitive function by way of contributing to and increasing cognitive reserve (Stern, 2012). In fact, number of years of education (early and late life) and leisure cognitive activity are two factors used to indirectly measure cognitive reserve in older adults (Meng & D'arcy, 2012; Nucci, Mapelli, & Mondini, 2012; Opdebeeck, Martyr, & Clare, 2016; Peeters, Kenny, & Lawlor, 2020; Thow et al., 2018). Taken together, a generalized recommendation of increasing education and cognitive activity is a feasible target for older adults to develop resilience against multiple risk factors for cognitive decline.

Notably, there were other domain-specific commonalities regarding the constellations of factors associated with resilience. A common factor contributing to memory resilience across the two physical health adversities was alcohol use. This was also noted as a predictor of memory resilience for female *CLU* risk carriers (McDermott et al., 2017). Most prior studies suggest an inverted u-shaped relationship, indicating that low and moderate alcohol use is associated with cognitively protective effects, whereas heavy use is associated with adverse cognitive effects (Anstey, Mack, & Cherbuin, 2009; Carrigan & Barkus, 2016; Piumatti, Moore, Berridge, Sakar, & Gallacher, 2018; Sachdeva, Chandra, Choudhary, Dayal, & Anand, 2016). We note that in our research and the study done by McDermott and colleagues (2017), the alcohol use variable was dichotomized into yes or no categories and does not include information about the amount of consumption. Therefore, while outside the scope of the present reserach, future research could aim to quantify the amount of alcohol use that contributes to memory resilience.

Younger age was a common predictor of EF resilience across the the two health adversities. Recently, younger age has been identified as a discriminating factor of EF trajectories in older non-demented adults (Caballero et al., 2020). Specifically, younger age distinguished between EF trajectories of older adults classified in a highest-level-and-stable group versus a lowest-level-and-declining group. As EF is one of the most age-sensitive cognitive domains, with increasing age associated with structural changes in the prefrontal cortex and subsequent EF deficits, it makes sense that younger age would proffer resilience against the influence of frailty and mobility adversity for EF decline (Li, Vadaga, Bruce, & Lai, 2017).

Differences in Predictors of Resilience to Frailty and Low Mobility. Our results indicated notable diversity in the predictive profiles of resilience to each of the physical health adversities, and across the cognitive domains. For example, comparing predictors of frailty and mobility adversity, there were several commonalities for memory and EF resilience, but no common predictors of speed resilience. This result may indicate varying pathophysiologic underpinnings of frailty and low mobility that lend differentially to the neuropsychological effects of both domain-specific cognitive performance, and the factors that may foster cognitive resilience. Moreover, the variability in predictive factors supports the contentions that resilience may be the result of unique constellations of resources that vary across different domains of functioning (Staudinger & Greve, 2015). Notably, this diversity in predictive factors also suggests that resilience to adversity does not require specific factors or resources that are only available to certain individuals (e.g., those of younger age, females). In fact, there may be a variety of resilience-fostering factors from which individuals may select what is feasible for their individual situation and developmental processes.

In sum, the machine learning prediction analyses (RFA) indicated that multiple predictors discriminate between data-driven subclasses of cognitively resilient and non-resilient trajectories. As we increase our understanding of factors that foster cognitive resilience, in the face of adversities, it may be possible to develop a systematic approach to fostering resilience across the lifespan (Staudinger & Greve, 2016).

Future Directions

The strengths and limitations of each study have been discussed extensively in the separate chapters, so rather than repeating their commonalities here, this section will focus on future directions and suggestions for research in this newly emerging field. First, an enhanced conceptual and operational understanding of resilience (in general) and cognitive resilience (in particular) will contribute to further advancement in this promising area (Anstey & Dixon, in press; Dixon & Lachman, 2019). For the latter, we suggest an operational definition that would apply to examination of cognitive resilience within the context of multiple common aging-related adversities. Specifically, as used in this dissertation, we suggest that resilience be considered directly in the presence of objectively measureable adversities that present elevated risk for early or exacerbated cognitive decline. With this approach, cognitive resilience could be examined and compared across multiple aging-related adversities, perhaps especially those that present risk for neurodegenerative disease, such as AD. For example, future research could examine cognitive resilience in light of other detrimental physical health factors (e.g., obesity, diabetes).

Second, to developmentally contextualize resilience, research needs to consider individualized, longitudinal cognitive trajectories, across a wide band of aging. Notably, as suggested by Staudinger and Greve (2016; see also McFall et al., 2019), it will be important to determine which processes take their roots in early life and manifest in resilience constellations

in older age (e.g., early life education), and which practices can be fostered in later life (e.g., physical activity).

Third, it may be important for future research to consider (a) age-related changes in resilience, as well as (b) changes across time in predictors of resilience. The present research considered baseline predictors of resilience and examined age as a predictor of resilience. However, this may only be a small piece of the puzzle. Examining resilience across (a) age strata, and (b) predictive factors across multiple timepoints may indicate times or ages during which some predictive factors are more prevalent or influential than others. Additionally, examining resilience considering age groups of older adults may reveal differing patterns or predictors of resilience for differing age strata (see McFall et al., 2019 for an example of this analysis).

Fourth, future research should consider another important stratification variable, namely sex or gender. We are aware of only one cognitive resilience study that stratifies by sex (McDermott et al., 2017). Sex has been identified as one of three main risk factors for AD (Riedel et al., 2017) yet there is a paucity of research directly considering sex effects in cognitive aging research. Recently, a best-practice model for the integration of sex and gender in cognitive aging research has been incorporated into the Canadian Consortium on Neurodegeneration in Aging (CCNA) (Tierney et al., 2017). Tierney and colleagues (2017) strongly recommend that research designs be balanced between males and females, and that sex be considered as a main variable of interest. Notably, our memory resilience to frailty results indicated that there are factors predictive of resilience specific to females. However, we were unable to conduct the same analysis with the small sample of males in our study. Future research would be well

advised to consider a sex-balanced research design as there may be differential sex-specific mechanisms underlying cognitive resilience (Dixon & Lachman, 2019).

Fifth, it will be important to determine networks of interacting factors that foster (or suppress) cognitive resilience over time. While our research considered a set of individual predictors of resilience across each cognitive domain, there may be factors that work together or can be clustered into composites. For example, it may be possible that some factors may synergistically contribute to resilience (e.g., engaged lifestyle). Therefore, considering those collectively may yield differing results than when considered individually. A similar approach (assessing dementia risk) was done using polygenic risk and healthy lifestyle scores (Lourida et al., 2019). Conceptually, this approach to dementia risk may be used to inform the field of cognitive resilience.

Sixth, our results do not make any determinations of causality, nor of the neurological correlates of resilience. Instead, our research contributes to the foundational work in cognitive resilience. Specifically, we establish this emerging phenomenon by empirically defining cognitive resilience to common aging-related physical health adversities and examine possible age-associated factors predictive of resilience. Future research in this emerging area may examine the neural basis for cognitive resilience, including the distinct domain-specific neural correlates that are associated with the distinct results we see in this research. Finally, future research will need to examine how cognitive resilience can be altered by interventions targeting at increasing or developing resilience. While there is great potential in this novel concept, interventions targeting resilience have yet to be developed and tested. Notably, optimizing resilience across the lifespan may prove to be a feasible target for older adults at risk for cognitive impairment.

In conclusion, the present research established variability in level and slope of two common aging-related physical health adversities, both of which contribute to cognitive decline and impairment, namely frailty and mobility. In the second chapter, we examined the influence of frailty on cognitive performance and change as moderated by sex and *APOE* genetic risk. In the third and fourth chapters, we provided evidence that two classes of higher and lower performance can be empirically derived from broad distributions of frailty and mobility trajectories. Subsequently, in the latter chapters, we used the frailty and low mobility classes to operationally define and objectively determine cognitive resilience across three age-sensitive domains of cognition. Specifically, we identified several predictive factors of resilience to two physical health adversities, proffering both generalized and specific means of fostering cognitive resilience, despite risk for later cognitive impairment or even AD. Accordingly, identifying common predictors of cognitive resilience has the potential for generalized recommendations to be made to promote brain and cognitive health for older adults. Specific to the results of the present and emerging resilience research, these generalized recommendations currently include increasing education and cognitive activity. Furthermore, this research detected unique factors that were predictive of resilience to the two physical health adversities. This may foster future opportunities for precision interventions for older adults (Dixon & Lachman, 2019). In sum, identifying and quantifying cognitive resilience in the context of common aging-related adversities offers immense potential as an AD risk-reduction target for older adults.

Table 5-1

Predictive Factors of Cognitive Resilience Across Physical Health Adversity and Cognitive Domain

Predictive Factors	Frailty			Low Mobility		
	Memory	*Speed*	*EF*	*Memory*	*Speed*	*EF*
1. Age			X		X	X
2. Education	X		X	X	X	
3. Sex	X					
4. Marital Status	X					
5. Living Status						
6. Pet Ownership						
7. Alcohol Use	X			X		
8. Cognitive Activity	X	X	X	X		X
9. Social Activity					X	X
10. Volunteer Activity						X
11. APOE				X		
12. BDNF						
13. Physical Activity				X		
14. Diabetes						
15. Depressive Symptoms				X		
16. Peak Flow				X	X	
17. Subjective Health					X	
18. Anti-inflammatory						
19. Grip Strength						X
20. Pulse Pressure						
21. BMI						

Note. Abbreviations: *APOE*, Apolipprotein E; *BDNF*, brain–derived neurotrophic factor; BMI, body mass index. The first 12 predictors were used in Chapters Three and Four. The latter predictors were included in Chapter Four.

References

Abdulla, A., Adams, N., Bone, M., Elliott, A. M., Gaffin, J., Jones, D., Knaggs, R., Martin, D., Sampson, L., Schofield, P., & British Geriatric Society (2013). Guidance on the management of pain in older people. *Age and Ageing, 42*(Suppl 1), i1–i57. doi:10.1093/ageing/afs200

Aiello Bowles, E. J., Crane, P. K., Walker, R. L., Chubak., J., LaCroix, A. Z., Anderson, M. L., Rosenberg, D., Keene, C. D., & Larson, E. B. (2019). Cognitive resilience to Alzheimer's disease pathology in the human brain. *Journal of Alzheimer's Disease, 68*(3), 1071-1083. doi:10.3233/JAD-180942

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008

Amblàs-Novellas, J., Martori, J. C., Espaulella, J., Oller, R., Molist-Brunet, N., Inzitari, M., & Romero-Ortuno, R. (2018). Frail-VIG index: a concise frailty evaluation tool for rapid geriatric assessment. *BMC geriatrics, 18*(1), 29. doi:10.1186/s12877-018-0718-2

Amini, R., Sahli, M., & Ganai, S. (2020). Cigarette smoking and cognitive function among older adults living in the community. *Aging, Neuropsychology, and Cognition*, 1-16. doi:10.1080/13825585.2020.1806199

Andrew, M. K., & Keefe, J. M. (2014). Social vulnerability from a social ecology perspective: A cohort study of older adults from the National Population Health Survey of Canada. *BMC Geriatrics, 14*(1), 90. doi:10.1186/1471-2318-14-90

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., & Buckner, R. L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron, 56*(5), 924-935. doi:10.1016/j.neuron.2007.10.038

Anstey, K. J. (2013). Optimizing cognitive development over the life course and preventing cognitive decline: Introducing the Cognitive Health Environment Life Course Model (CHELM). *International Journal of Behavioral Development, 38*(1), 1-10. doi:10.1177/0165025413512255

Anstey, K. J., Cherbuin, N., Budge, M., & Young, J. (2011). Body mass index in midlife and late-life as a risk factor for dementia: A meta-analysis of prospective studies. *Obesity Reviews, 12*(5), e426-e437. doi:10.1111/j.1467-789X.2010.00825.x

Anstey, K. J., Ee, N., Eramudugolla, R., Jagger, C., & Peters, R. (2019). A Systematic review of Meta-Analyses that evaluate risk factors for dementia to evaluate the quantity, quality, and global representativeness of evidence. *Journal of Alzheimer's Disease, 70*, S165-S186. doi:10.3233/JAD-190181

Anstey, K. J., Mack, H. A., & Cherbuin, N. (2009). Alcohol consumption as a risk factor for dementia and cognitive decline: Meta-analysis of prospective studies. *The American Journal of Geriatric psychiatry, 17*(7), 542-555. doi:10.1097/JGP.0b013e3181a2fd07

Anstey, K.J., & Dixon, R.A. (in press). *Resilience in mid-life and aging*. In K.W. Schaie & S.L. Willis (Eds.), Handbook of the psychology of aging (9th ed.). Amsterdam: Elsevier.

Antonovsky, A. (1996). The salutogenic model as a theory to guide health promotion. *Health Promotion International, 11*(1), 11-18. doi:10.1093/heapro/11.1.11

Armstrong, J., Mitnitski, A., Launer, L., White, L., & Rockwood, K. (2013). Frailty in relation to late-life cognition: Initial results from the Honolulu-Asian Aging Study. *Alzheimer's & Dementia, 9*(4), P611. doi:10.1016/j.jalz.2013.05.1230

Arnold, S. E., Louneva, N., Cao, K., Wang, L.-S., Han, L.-Y., Wolk, D. A., Negash, S., Leurgans, S. E., Schneider, J. A., Buchman, A. S., Wilson, R. S., & Bennett, D. A. (2013). Cellular, synaptic, and biochemical features of resilient cognition in Alzheimer's disease. *Neurobiology of Aging, 34*(1), 157-168. doi:10.1016/j.neurobiolaging.2012.03.004

Au, B., Dale-McGrath, S., & Tierney, M. C. (2017). Sex differences in the prevalence and incidence of mild cognitive impairment: A meta-analysis. *Ageing Research Reviews, 35,* 176-199. doi:10.1016/j.arr.2016.09.005

Ayers, E. I., Verghese, J., & Allali, G. (2015). Motoric cognitive risk syndrome subtypes and cognitive profiles. *The Journals of Gerontology: Series A, 71*(3), 378-384. doi:10.1093/gerona/glv092

Bäckman, L., Jones, S., Berger, A. K., Laukka, E. J., & Small, B. J. (2005). Cognitive impairment in preclinical Alzheimer's disease: A meta-analysis. *Neuropsychology, 19*(4), 520-531. doi:10.1037/0894-4105.19.4.520

Baltes, P. B. (1987). Theoretical propositions of life-span developmental psychology: On the dynamics between growth and decline. *Developmental Psychology, 23*(5), 611-626.

Baltes, P. B. (1997). On the incomplete architecture of human ontogeny: Selection, optimization, and compensation as foundation of developmental theory. *American Psychologist, 52*(4), 366.

Baltes, P. B., Lindenberger, U., & Staudinger, U. M. (2006). Life span theory in developmental psychology. In R. M. Lerner & W. Damon (Eds.), *Handbook of child psychology: Theoretical models of human development* (pp. 569-664). John Wiley & Sons Inc.

Baltes, P. B., Staudinger, U. M., & Lindenberger, U. (1999). Lifespan psychology: Theory and application to intellectual functioning. *Annual Review of Psychology, 50*(1), 471-507. doi:10.1146/annurev.psych.50.1.471

Bandeen-Roche, K., Buta, B., Walston, J. D., Huang, J., Xue, Q.-L., Kalyani, R. R., Varadhan, R., Xue, Q., Waltson, J. D., & Kasper, J. D. (2015). Frailty in older adults: A nationally representative profile in the United States. *The Journals of Gerontology: Series A, 70*(11), 1427-1434. doi:10.1093/gerona/glv133

Barha, C., Best, J., Liu-Ambrose, T., & Rosano, C. (2018). BDNF VAL66MET Polymorphism, sex and resilience to cognitive and physical activity declines. *Innovation in Aging, 2(*suppl_1), 93-93. doi:10.1093/geroni/igy023.353

Bathina, S., & Das, U. N. (2015). Brain-derived neurotrophic factor and its clinical implications. *Archives of Medical Science: AMS, 11*(6), 1164-1178. doi:10.5114/aoms.2015.56342

Baudic, S., Barba, G. D., Thibaudet, M. C., Smagghe, A., Remy, P., & Traykov, L. (2006). Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Archives of Clinical Neuropsychology, 21(*1), 15-21. doi:10.1016/j.acn.2005.07.002

Beard, J. R., Officer, A., de Carvalho, I. A., Sadana, R., Pot, A. M., Michel, J.-P., Lloyd-Sherlock, P., Epping-Jordan, J. E., Peeters, G. M. E. E., Mahanani, W. R., Thiyagarajan, J. A., & Chatterji, S. (2016). The World report on ageing and health: A policy framework for healthy ageing. *The Lancet, 387*(10033), 2145-2154. doi:10.1016/S0140-6736(15)00516-4

Beekman, A. T., Copeland, J., & Prince, M. J. (1999). Review of community prevalence of depression in later life. *The British Journal of Psychiatry, 174*(4), 307-311. doi:10.1192/bjp.174.4.307

Bennett, I. J., & Madden, D. J. (2014). Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. *Neuroscience, 276,* 187-205. doi:10.1016/j.neuroscience.2013.11.026

Berlin, K. S., Williams, N. A., & Parra, G. R. (2014). An introduction to latent variable mixture modeling (part 1): Overview and cross-sectional latent class and latent profile analyses. *Journal of Pediatric Psychology, 39*(2), 174-187. doi:10.1093/jpepsy/jst084

Berryman, N., Bherer, L., Nadeau, S., Lauzière, S., Lehr, L., Bobeuf, F., Kergoat, M. J., Vu, T. T. M., & Bosquet, L. (2013). Executive functions, physical fitness and mobility in well-functioning older adults. *Experimental Gerontology, 48*(12), 1402-1409. doi:10.1016/j.exger.2013.08.017

Bherer, L. (2015). Cognitive plasticity in older adults: Effects of cognitive training and physical exercise. *Annals of the New York Academy of Sciences, 1337*(1), 1-6. doi:10.1111/nyas.12682

Bizier, C., Fawcett, G., & Gilbert, S. (2016). *Mobility disabilities among Canadians aged 15 years and older, 2012*. https://www150.statcan.gc.ca/n1/en/pub/89-654-x/89-654-x2016005-eng.pdf?st=sM981Hd6

Blazer, D. G., Yaffe, K., & Karlawish, J. (2015). Cognitive aging: A report from the institute of medicine. *Journal of American Medical Association, 313*(21), 2121-2122. doi:10.1001/jama.2015.4380

Blazer, D. G., Yaffe, K., & Liverman, C. T. (2015). *Cognitive aging: Progress in understanding and opportunities for action.* National Academies Press Washington, DC.

Blodgett, J. M., Theou, O., Mitnitski, A., Howlett, S. E., & Rockwood, K. (2019). Associations between a laboratory frailty index and adverse health outcomes across age and sex. *Aging Medicine, 2*(1), 11-17. doi:10.1002/agm2.12055

Bohn, L., McFall, G. P., Wiebe, S. A., & Dixon, R. A. (2020). Body mass index predicts cognitive aging trajectories selectively for females: Evidence from the Victoria Longitudinal Study. *Neuropsychology, 34*(4), 388–403. doi:10.1037/neu0000617

Borelli, W. V., Schilling, L. P., Radaelli, G., Ferreira, L. B., Pisani, L., Portuguez, M. W., & da Costa, J. C. (2018). Neurobiological findings associated with high cognitive performance in older adults: A systematic review. *International Psychogeriatrics, 30*(12), 1813. doi:10.1017/S1041610218000431

Borgeest, G. S., Henson, R. N., Shafto, M., Samu, D., Cam, C. A. N., & Kievit, R. A. (2020). Greater lifestyle engagement is associated with better age-adjusted cognitive abilities. *PLOS ONE, 15*(5), e0230077. doi:10.1371/journal.pone.0230077

Borges, S. d. M., Radanovic, M., & Forlenza, O. V. (2018). Correlation between functional mobility and cognitive performance in older adults with cognitive impairment. *Aging, Neuropsychology, and Cognition, 25*(1), 23-32. doi:10.1080/13825585.2016.1258035

Boyle, P. A., Buchman, A. S., Wilson, R. S., Leurgans, S. E., & Bennett, D. A. (2010). Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *Journal of the American Geriatric Society, 58*(2), 248-255. doi:10.1111/j.1532-5415.2009.02671.x

Brainerd, C. J., Reyna, V. F., Petersen, R. C., Smith, G. E., & Taub, E. S. (2011). Is the apolipoprotein e genotype a biomarker for mild cognitive impairment? Findings from a nationally representative study. *Neuropsychology, 25*(6), 679-689. doi:10.1037/a0024483

Brayne, C., & Richard, E. (2019). Prevention of cognitive decline: A goal in sight? *Journal of Alzheimer's Disease, 70*, S11-S14. doi:10.3233/JAD-190448

Brown, C. L., Robitaille, A., Zelinski, E. M., Dixon, R. A., Hofer, S. M., & Piccinin, A. M. (2016). Cognitive activity mediates the association between social activity and cognitive performance: A longitudinal study. *Psychology and Aging, 31*(8), 831–846. doi:10.1037/pag0000134

Buchman, A. S., Boyle, P. A., Wilson, R. S., Beck, T. L., Kelly, J. F., & Bennett, D. A. (2009). Apolipoprotein E e4 allele is associated with more rapid motor decline in older persons. *Alzheimer Disease and Associated Disorders, 23*(1), 63-69. doi:10.1097/wad.0b013e31818877b5

Buchman, A. S., Yu, L., Boyle, P. A., Schneider, J. A., De Jager, P. L., & Bennett, D. A. (2016). Higher brain BDNF gene expression is associated with slower cognitive decline in older adults. *Neurology, 86*(8), 735-741. doi:10.1212/WNL.0000000000002387

Buchman, A., Boyle, P. A., Wilson, R. S., Tang, Y., & Bennett, D. A. (2007). Frailty is associated with incident Alzheimer’s disease and cognitive decline in the elderly. *Psychosomatic Medicine, 69*. doi:10.1097/psy.0b013e318068de1d

Buchman, A., Wilson, R. S., Boyle, P. A., Tang, Y., Fleischman, D. A., & Bennett, D. A. (2007). Physical activity and leg strength predict decline in mobility performance in older persons. *Journal of the American Geriatric Society, 55*(10), 1618-1623. doi:10.1111/j.1532-5415.2007.01359.x

Buckner, R. L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*(1), 195-208. doi:10.1016/j.neuron.2004.09.006

Burgess, P. W., & Shallice, T. (1997). *The Hayling and Brixton Tests*. Bury St. Edmunds, United Kingdom: Thames Valley Test Company.

Butler, M., McCreedy, E., Nelson, V. A., Desai, P., Ratner, E., Fink, H. A., Hemmy, L. S., McCarten, J. R., Barclay, T. R., Brasure, M., Davila, H., & Kane, R. L. (2018). Does cognitive training prevent cognitive decline?: A systematic review. *Annals of Internal Medicine, 168*(1), 63-68. doi:10.7326/M17-1531

Caballero, H. S., McFall, G. P., Wiebe, S. A., & Dixon, R. A. (2020). Integrating three characteristics of executive function in non-demented aging: Trajectories, classification, and biomarker predictors. *Journal of the International Neuropsychological Society*, 1-14. doi:10.1017/S1355617720000703

Callisaya, M. L., Beare, R., Moran, C., Phan, T., Wang, W., & Srikanth, V. K. (2019). Type 2 diabetes mellitus, brain atrophy and cognitive decline in older people: A longitudinal study. *Diabetologia, 62*(3), 448-458. doi:10.1007/s00125-018-4778-9

Callisaya, M. L., Srikanth, V. K., Wood, A. G., Thrift, A. G., Blizzard, C. L., & Wardill, T. (2015). Longitudinal relationships between cognitive decline and gait slowing: The Tasmanian Study of Cognition and Gait. *The Journals of Gerontology: Series A, 70*(10), 1226-1232. doi:10.1093/gerona/glv066

Camicioli, R., Howieson, D., Oken, B., Sexton, G., & Kaye, J. (1998). Motor slowing precedes cognitive impairment in the oldest old. *Neurology, 50(*5), 1496. doi:10.1212/WNL.50.5.1496

Canevelli, M., Cesari, M., & van Kan, G. A. (2015). Frailty and cognitive decline: How do they relate*? Current Opinion in Clinical Nutrition & Metabolic Care, 18*(1), 43-50. doi:10.1097/MCO.0000000000000133

Carrigan, N., & Barkus, E. (2016). A systematic review of the relationship between psychological disorders or substance use and self-reported cognitive failures. *Cognitive neuropsychiatry, 21*(6), 539-564. doi:10.1080/13546805.2016.1250620

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Reports, 100(*2), 126–131.

Cavallo, M., Zanalda, E., Johnston, H., Bonansea, A., & Angilletta, C. (2016). Cognitive training in a large group of patients affected by early-stage Alzheimer's disease can have long-lasting effects: A case-control study. *Brain Impairment, 17(*2), 182-192. doi:10.1017/BrImp.2016.2

Centers for Disease Control and Prevention. (2013). QuickStats: Number of Deaths from 10 Leading Causes—National Vital Statistics System, United States, 2010. *Morbidity and Mortality Weekly Report, 2(*08), 155. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6208a8.htm

Cesari, M., Gambassi, G., Abellan van Kan, G., & Vellas, B. (2014). The frailty phenotype and the frailty index: Different instruments for different purposes. *Age and Ageing, 43*(1), 10-12. doi:10.1093/ageing/aft160

Cesari, M., Prince, M., Thiyagarajan, J. A., De Carvalho, I. A., Bernabei, R., Chan, P., Gutierrez-Robledo, L. M., Michel, J.-P., Morley, J. E., Ong, P., Manas, L. R., Sinclair, A., Won, C. W., Beard, J., & Vellas, B. (2016). Frailty: An emerging public health priority. *Journal of*

the American Medical Directors Association, 17(3), 188-192. doi:10.1016/j.jamda.2015.12.016

Chamberlain, A. M., Finney Rutten, L. J., Manemann, S. M., Yawn, B. P., Jacobson, D. J., Fan, C., Grossardt, B. R., Roger, V. L., & St Sauver, J. L. (2016). Frailty Trajectories in an Elderly Population-Based Cohort. *Journal of the American Geriatrics Society, 64*(2), 285-292. doi:10.1111/jgs.13944

Chapman, S. B., Spence, J. S., Aslan, S., & Keebler, M. W. (2017). Enhancing innovation and underlying neural mechanisms via cognitive training in healthy older adults. *Frontiers in Aging Neuroscience, 9*, 314. doi:10.3389/fnagi.2017.00314

Chawla, N. V., Bowyer, K. W., Hall, L. O., & Kegelmeyer, W. P. (2002). SMOTE: synthetic minority over-sampling technique. *Journal of Artificial Intelligence Research, 16*, 321-357. doi:10.1613/jair.953

Chen, X., Mao, G., & Leng, S. X. (2014). Frailty syndrome: An overview. *Clinical Interventions in Aging, 9*, 433-441. doi:10.2147/CIA.S45300

Cheng, S.-T. (2016). Cognitive reserve and the prevention of dementia: The role of physical and cognitive activities. *Current Psychiatry Reports, 18*(9), 85. doi:10.1007/s11920-016-0721-2

Cherry, K. E., Walker, E. J., Brown, J. S., Volaufova, J., LaMotte, L. R., Welsh, D. A., SU, J. L., Jazwinski, S. M., Ellis, R., Wood, R. H., & Frisard, M. I. (2013). Social engagement and health in younger, older, and oldest-old adults in the Louisiana Healthy Aging Study. *Journal of Applied Gerontology, 32*(1), 51-75. doi:10.1177/0733464811409034

Chopra, S., Shaw, M., Shaw, T., Sachdev, P. S., Anstey, K. J., & Cherbuin, N. (2018). More highly myelinated white matter tracts are associated with faster processing speed in healthy adults. *NeuroImage, 171*, 332-340. doi:10.1016/j.neuroimage.2017.12.069

Christensen, H., Dear, K. B., Anstey, K. J., Parslow, R. A., Sachdev, P., & Jorm, A. F. (2005). Within-occasion intraindividual variability and preclinical diagnostic status: Is intraindividual variability an indicator of mild cognitive impairment? *Neuropsychology, 19*(3), 309-317. doi:10.1037/0894-4105.19.3.309

Christensen, H., Mackinnon, A. J., Korten, A., & Jorm, A. F. (2001). The "common cause hypothesis" of cognitive aging: evidence for not only a common factor but also specific associations of age with vision and grip strength in a cross-sectional analysis. *Psychology and Aging, 16*(4), 588. doi:10.1037//0882-7974.16.4.588

Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. *Lancet., 381*. doi:10.1016/s0140-6736(12)62167-9

Clouston, S. A. P., Smith, D. M., Mukherjee, S., Zhang, Y., Hou, W., Link, B. G., & Richards, M. (2020). Education and cognitive decline: An integrative analysis of global longitudinal studies of cognitive aging. *The Journals of Gerontology: Series B, 75*(7), e151-e160. doi:10.1093/geronb/gbz053

Coelho, F. M., Pereira, D. S., Lustosa, L. P., Silva, J. P., Dias, J. M. D., Dias, R. C. D., Queiroz, B. Z., Teixeira, A. L., Teixeira, M. M., & Pereira, L. S. M. (2012). Physical therapy intervention (PTI) increases plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly women. *Archives of Gerontology and Geriatrics, 54*(3), 415-420. doi:10.1016/j.arhcger.2011.05.014

Cooper, R., Kuh, D., & Hardy, R. (2010). Objectively measured physical capability levels and mortality: Systematic review and meta-analysis. *BMJ, 341*, c4467. doi:10.1136/bmj.c4467

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., Roses, A. D., Haines, J. L., & Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science, 261*(5123), 921-923. doi:10.1126/science.8346443

Corrada, M. M., Berlau, D. J., & Kawas, C. H. (2012). A population-based clinicopathological study in the oldest-old: The 90+ study. *Current Alzheimer Research, 9*(6), 709–717. doi:10.2174/156720512801322537

Courtin, E., & Knapp, M. (2017). Social isolation, loneliness and health in old age: A scoping review. *Health & Social Care in the Community, 25*(3), 799-812. doi:10.1111/hsc.12311

Courtney-Long, E. A., Carroll, D. D., Zhang, Q. C., Stevens, A. C., Griffin-Blake, S., Armour, B. S., & Campbell, V. A. (2015). Prevalence of disability and disability type among adults—United States, 2013. *Morbidity and Mortality Weekly Report, 64*(29), 777.

Covell, G. E. S., Hoffman-Snyder, C. R., Wellik, K. E., Woodruff, B. K., Geda, Y. E., Caselli, R. J., Demaerschalk, B. M., & Wingerchuk, D. M. (2015). Physical activity level and future risk of mild cognitive impairment or dementia: A critically appraised topic. *The Neurologist, 19*(3), 89-91. doi:10.1097/NRL.0000000000000013

Crawford, A., Hollingsworth, H. H., Morgan, K., & Gray, D. B. (2008). People with mobility impairments: Physical activity and quality of participation. *Disability and Health Journal, 1(*1), 7-13. doi:10.1016/j.dhjo.2007.11.004

Cummings, J., Lee, G., Ritter, A., & Zhong, K. (2018). Alzheimer's disease drug development pipeline: 2018. *Alzheimer's & Dementia: Translational Research & Clinical Interventions, 4*, 195-214. doi:10.1016/j.trci.2018.03.009

Dahlin, E., Nyberg, L., Bäckman, L., & Neely, A. S. (2008). Plasticity of executive functioning in young and older adults: Immediate training gains, transfer, and long-term maintenance. *Psychology and Aging, 23*(4), 720-730. doi:10.1037/a0014296

Damoiseaux, J. S., Beckmann, C. F., Arigita, E. J. S., Barkhof, F., Scheltens, P., Stam, C. J., & Rombouts, S. A. R. B. (2007). Reduced resting-state brain activity in the “default network” in normal aging. *Cerebral Cortex, 18*(8), 1856-1864. doi:10.1093/cercor/bhm207

Dause, T. J., & Kirby, E. D. (2019). Aging gracefully: Social engagement joins exercise and enrichment as a key lifestyle factor in resistance to age-related cognitive decline. *Neural Regeneration Research, 14*(1), 39–42. doi:10.4103/1673-5374.243698

Davis, D. H. J., Rockwood, M. R. H., Mitnitski, A. B., & Rockwood, K. (2011). Impairments in mobility and balance in relation to frailty. *Archives of Gerontology and Geriatrics, 53*(1), 79-83. doi:10.1016/j.archger.2010.06.013

Davis, J. C., Bryan, S., Best, J. R., Li, L. C., Hsu, C. L., Gomez, C., Vertes, K. A., & Liu-Ambrose, T. (2015). Mobility predicts change in older adults’ health-related quality of life: Evidence from a Vancouver falls prevention prospective cohort study. *Health and Quality of Life Outcomes, 13*(1), 101. doi:10.1186/s12955-015-0299-0

de Frias, C. M., Dixon, R. A., & Strauss, E. (2009). Characterizing executive functioning in older special populations: From cognitively elite to cognitively impaired. *Neuropsychology, 23*(6), 778-791. doi:10.1037/a0016743

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E.., Houlihan, L. M., Marioni R. E., Penke, L., Rafnsson, S. B., & Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin, 92(*1), 35-152. doi:10.1093/bmb/ldp033

Deckers, K., Nooyens, A., van Boxtel, M., Verhey, F., Verschuren, M., & Köhler, S. (2019). Gender and educational differences in the association between lifestyle and cognitive decline over 10 Years: The Doetinchem Cohort Study. *Journal of Alzheimer's Disease, 70,* S31-S41. doi:10.3233/JAD-180492

Dekhtyar, S., Wang, H.-X., Fratiglioni, L., & Herlitz, A. J. (2016). Childhood school performance, education and occupational complexity: A life-course study of dementia in the Kungsholmen Project. *International Journal of Epidemiology, 45*(4), 1207-1215. doi:10.1093/ije/dyw008

D'Elia, L. F., Satz, P., Uchiyama, C. L., & White, T. (1996). *Color Trails Test: Professional Manual.* Odessa, FL: Psychological Assessment Resources.

Demnitz, N., Zsoldos, E., Mahmood, A., Mackay, C. E., Kivimäki, M., Singh-Manoux, A., Dawes, H., Johansen-Berg, H., Ebmeier, K. P., & Sexton, C. E. (2017). Associations between mobility, cognition, and brain structure in healthy older adults. *Frontiers in Aging Neuroscience, 9*, 155-155. doi:10.3389/fnagi.2017.00155

Dent, E., Kowal, P., & Hoogendijk, E. O. (2016). Frailty measurement in research and clinical practice: A review. *European Journal of Internal Medicine, 31*, 3-10. doi:10.1016/j.ejim.2016.03.007

Desjardins-Crépeau, L., Berryman, N., Vu, T. T. M., Villalpando, J. M., Kergoat, M.-J., Li, K. Z., Bosquet, L., & Bherer, L. (2014). Physical functioning is associated with processing speed and executive functions in community-dwelling older adults. *The Journals of*

Gerontology Series B: Psychological Sciences and Social Sciences, 69(6), 837-844. doi:10.1093/geronb/gbu036

Dixon, R. A. (2000). Concepts and mechanisms of gains in cognitive aging. In D. Park & N. Schwartz (Eds.), *Cognitive Aging: A primer* (pp. 23 – 42). New York, NY, US: Psychology Press.

Dixon, R. A. (2011). Enduring theoretical themes in psychological aging: Derivation, functions, perspectives, and opportunities. In K. W. Schaie & S. L Willis (Eds.), *Handbook of the psychology of aging, 7th ed.* (pp. 3-23). San Diego, CA, US: Elsevier Academic Press.

Dixon, R. A., & de Frias, C. M. (2004). The Victoria Longitudinal Study: From characterizing cognitive aging to illustrating changes in memory compensation. *Aging, Neuropsychology, and Cognition, 11*(2-3), 346-376. doi:10.1080/13825580490511161

Dixon, R. A., & de Frias, C. M. (2007). Mild memory deficits differentially affect 6-year changes in compensatory strategy use. *Psychology of Aging, 22*(3), 632-638. doi:10.1037/0882-7974.22.3.632

Dixon, R. A., Garrett, D. D., Lentz, T. L., MacDonald, S. W., Strauss, E., & Hultsch, D. F. (2007). Neurocognitive markers of cognitive impairment: exploring the roles of speed and inconsistency. *Neuropsychology, 21*(3), 381-399. doi:10.1037/0894-4105.21.3.381

Dixon, R. A., Small, B., MacDonald, S. W., & McArdle, J. J. (2012). Yes, memory declines with aging—but when, how, and why? In M. Naveh-Benjamin & N. Ohta (Eds.), *Memory and Aging: Current Issues and Future Directions* (pp. 325-347). New York: Psychology Press.

Dixon, R.A., Lachman, M.E. (2019). Risk and protective factors in cognitive aging: Advances in assessment, prevention, and promotion of alternative pathways. In G. R. Samanez-Larkin

(Ed.) *The aging brain: Functional adaptation across adulthood* (pp. 217-263). Washington DC: American Psychological Association Books. doi:10.1037/0000143-009

Doi, T., Shimada, H., Makizako, H., Tsutsumimoto, K., Uemura, K., Anan, Y., & Suzuki, T. (2014). Cognitive function and gait speed under normal and dual-task walking among older adults with mild cognitive impairment. *BMC Neurology, 14,* 67-67. doi:10.1186/1471-2377-14-67

Donovan, N. J., Wu, Q., Rentz, D. M., Sperling, R. A., Marshall, G. A., & Glymour, M. M. (2017). Loneliness, depression and cognitive function in older US adults. *International Journal of Geriatric Psychiatry, 32(*5), 564-573. doi:10.1002/gps.4495

Douglas, H., Georgiou, A., & Westbrook, J. (2017). Social participation as an indicator of successful aging: An overview of concepts and their associations with health. *Australian Health Review, 41*(4), 455-462. doi:10.1071/AH16038

Duda, B. M., & Sweet, L. H. (2020). Functional brain changes associated with cognitive training in healthy older adults: A preliminary ALE meta-analysis. *Brain Imaging and Behavior, 14*(4), 1247-1262. doi:10.1007/s11682-019-00080-0

Duggan, E. C., Graham, R. B., Piccinin, A. M., Jenkins, N. D., Clouston, S., Muniz-Terrera, G., & Hofer, S. M. (2020). Systematic review of pulmonary function and cognition in aging. *The Journals of Gerontology: Series B, 75*(5), 937-952. doi:10.1093/geronb/bgy128

Dumurgier, J., Artaud, F., Touraine, C., Rouaud, O., Tavernier, B., Dufouil, C., Singh-Manoux, A., Tzourio, C., & Elbaz, A. (2016). Gait speed and decline in gait speed as predictors of incident dementia. *The Journals of Gerontology: Series A, 72*(5), 655-661. doi:10.1093/gerona/glw110

Eckert, M. (2011). Slowing down: Age-related neurobiological predictors of processing speed. *Frontiers in Neuroscience, 5,* 25. doi:10.3389/fnins.2011.00025

Eckert, M. A., Keren, N. I., Roberts, D. R., Calhoun, V. D., & Harris, K. C. (2010). Age-related changes in processing speed: Unique contributions of cerebellar and prefrontal cortex. *Frontiers in Human Neuroscience, 4,* 10-10. doi:10.3389/neuro.09.010.2010

Edwards, J. D., Xu, H., Clark, D. O., Guey, L. T., Ross, L. A., & Unverzagt, F. W. (2017). Speed of processing training results in lower risk of dementia. *Alzheimer's & Dementia: Translational Research & Clinical Interventions, 3*(4), 603-611. doi:10.1016/j.trci.2017.09.002

Eeles, E., & Choy, N. L. (2015). Frailty and mobility. *Interdisiplinary Topics in Gerontology and Geriatrics, 41*, 107-120. doi:10.1159/000381200

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., & Weinberger, D. R. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell, 112*(2), 257-269. doi:10.1016/S0092-8674(03)00035-7

Elias M. F., Goodell A. L., & Dore G. A. (2012). Hypertension and cognitive functioning. *Hypertension, 60*(2), 260-268. doi:10.1161/Hypertensionaha.111.186429

Emery, C. F., Finkel, D., & Pedersen, N. L. (2012). Pulmonary function as a cause of cognitive aging. *Psychological Science, 23(*9), 1024–1032. doi:10.1177/0956797612439422

Emmerzaal, T. L., Kiliaan, A. J., & Gustafson, D. R. (2015). 2003-2013: A decade of body mass index, Alzheimer's disease, and dementia. *Journal of Alzheimer's Disease, 43*, 739-755. doi:10.3233/JAD-141086

Enders-Slegers, M.-J., & Hediger, K. (2019). Pet ownership and human–animal interaction in an aging population: Rewards and challenges. *Anthrozoös, 32*(2), 255-265. doi:10.1080/08927936.2019.1569907

Erickson, K. I., Hillman, C. H., & Kramer, A. F. (2015). Physical activity, brain, and cognition. *Current Opinion in Behavioral Sciences, 4,* 27-32. doi:10.1016/j.cobeha.2015.01.005

Erickson, K. I., Miller, D. L., & Roecklein, K. A. (2012). The aging hippocampus: Interactions between exercise, depression, and BDNF. *The Neuroscientist, 18*(1), 82-97. doi:10.1177/1073858410397054

Etnier, J. L., Drollette, E. S., & Slutsky, A. B. (2019). Physical activity and cognition: A narrative review of the evidence for older adults. *Psychology of Sport and Exercise, 42*, 156-166. doi:10.1016/j.psychsport.2018.12.006

Fallah, N., Mitnitski, A., Searle, S. D., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2011). Transitions in frailty status in older adults in relation to mobility: A multistate modeling approach employing a deficit count. *Journal of the American Geriatrics Society, 59*(3), 524-529. doi:10.1111/j.1532-5415.2011.03300.x

Fan, L.-Y., Tzen, K.-Y., Chen, Y.-F., Chen, T.-F., Lai, Y.-M., Yen, R.-F., Huang, Y-Y., Shiue, C-Y., Yang, S-Y, & Chiu, M.-J. (2018). The relation between brain amyloid deposition, cortical atrophy, and plasma biomarkers in Amnesic Mild Cognitive Impairment and Alzheimer's Disease. *Frontiers in Aging Neuroscience, 10*, 175. doi:10.3389/fnagi.2018.00175

Fan, Y.-T., Fang, Y.-W., Chen, Y.-P., Leshikar, E. D., Lin, C.-P., Tzeng, O. J. L., Huang, H-W., & Huang, C.-M. (2019). Aging, cognition, and the brain: effects of age-related variation in

white matter integrity on neuropsychological function. *Aging & Mental Health, 23*(7), 831-839. doi:10.1080/13607863.2018.1455804

Feng, L., Ng, X. T., Yap, P., Li, J., Lee, T. S., Håkansson, K., Kua, E-H., Ng, T. P. (2014). Marital status and cognitive impairment among community-dwelling Chinese Older Adults: The role of gender and social engagement. *Dementia and Geriatric Cognitive Disorders Extra, 4*(3), 375-384. doi:10.1159/000358584

Ferreira, L., Tanaka, K., Santos-Galduróz, R. F., & Galduróz, J. C. F. (2015). Respiratory training as strategy to prevent cognitive decline in aging: A randomized controlled trial. *Journal of Clinical Interventions in Aging, 10*, 593–603. doi:10.2147/CIA.S79560

Ferrucci, L., Cooper, R., Shardell, M., Simonsick, E. M., Schrack, J. A., & Kuh, D. (2016). Age-related change in mobility: Perspectives from life course epidemiology and geroscience. *The Journals of Gerontology: Series A, 71*(9), 1184-1194. doi:10.1093/gerona/glw043

Fiacco, S., Mernone, L., & Ehlert, U. (2020). Psychobiological indicators of the subjectively experienced health status - findings from the Women 40+ Healthy Aging Study. *BMC Women's Health, 20(*1), 16. doi:10.1186/s12905-020-0888-x

Finkel, D., Bravell, M. E., & Pedersen, N. L. (2020). Role of motor function and lung function in pathways to ageing and decline. *Aging Clinical and Experimental Research*, 1-9. doi:10.1007/s40520-020-01494-3

Fong, J. H., & Kok, Z.-C. (2020). Does subjective health matter? Predicting overall and specific ADL disability incidence. *Archives of Gerontology and Geriatrics, 90*, 104169. doi:10.1016/j.archger.2020.104169

Fontes, A. P., & Neri, A. L. (2015). Resilience in aging: Literature review. *Ciencia & Saude Coletiva, 20*, 1475-1495. doi:10.1590/1413-81232015205.00502014

Foverskov, E., Glymour, M. M., Mortensen, E. L., Holm, A., Lange, T., & Lund, R. (2018). Education and cognitive aging: Accounting for selection and confounding in the Danish Registry-SHARE Data Linkage. *American Journal of Epidemiology, 187*(11), 2423-2430. doi:10.1093/aje/kwy162

Fratiglioni, L., & Wang, H. X. (2007). Brain reserve hypothesis in dementia. *Journal of Alzheimers Disease, 12*(1), 11-22. doi:10.3233/jad-2007-12103

Fratiglioni, L., Wang, H. X., Ericsson, K., Maytan, M., & Winblad, B. (2000). Influence of social network on occurrence of dementia: A community-based longitudinal study. *Lancet*, 355. doi:10.1016/S0140-6736(00)02113-9

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., & Gottdiener, J. (2001). Frailty in older adults: Evidence for a phenotype. *Journal of Gerontology: Series A*, 56. doi:10.1093/gerona/56.3.M146

Friedler, B., Crapser, J., & McCullough, L. (2015). One is the deadliest number: The detrimental effects of social isolation on cerebrovascular diseases and cognition. *Acta Neuropathologica, 129*(4), 493-509. doi:10.1007/s00401-014-1377-9

Friedmann, E., Gee, N. R., Simonsick, E. M., Studenski, S., Resnick, B., Barr, E., Kitner-Triolo, M., & Hackney, A. (2020). Pet ownership patterns and successful aging outcomes in community dwelling older adults. *Frontiers in Veterinary Science, 7*, 293. doi:10.3389/fvets.2020.00293

Gallo, J. J., Morales, K. H., Bogner, H. R., Raue, P. J., Zee, J., Bruce, M. L., & Reynolds, C. F. (2013). Long term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care. *BMJ*, 346. doi:10.1136/bmj.f2570

Ganguli, M., Dodge, H. H., & Mulsant, B. H. (2002). Rates and predictors of mortality in an aging, rural, community-based cohort: the role of depression. *Archives of General Psychiatry, 59*(11), 1046-1052. doi:10.1001/archpsych.59.11.1046

Gerdes, L. U., Jeune, B., Ranberg, K. A., Nybo, H., & Vaupel, J. W. (2000). Estimation of apolipoprotein E genotype-specific relative mortality risks from the distribution of genotypes in centenarians and middle-aged men: Apolipoprotein E gene is a "frailty gene," not a "longevity gene". *Genetic Epidemiology, 19*(3), 202-210. doi:10.1002/1098-2272(200010)19::3<202:aid-gepi2>3.0.co;2-q

Glisky, E. L. (2007). Changes in cognitive function in human aging. In D. R. Riddle (Ed.), *Brain Aging: Models, Methods, and Mechanisms (pp.* 3-20). CRC press/Taylor& Francis.

Goh, J. O., An, Y., & Resnick, S. M. (2012). Differential trajectories of age-related changes in components of executive and memory processes. *Psychology and Aging, 27*(3), 707-719. doi:10.1037/a0026715

Gonzales, M. M., Wang, C. P., Quiben, M., MacCarthy, D., Seshadri, S., Jacob, M., & Hazuda, H. (2020). Joint trajectories of cognition and gait speed in Mexican American and European American older adults: The San Antonio Longitudinal Study of Aging. *International Journal of Geriatric Psychiatry, 35*(8), 897-906. doi:10.1002/gps.5310

Gordon, E. H., Peel, N. M., Samanta, M., Theou, O., Howlett, S. E., & Hubbard, R. E. (2017). Sex differences in frailty: A systematic review and meta-analysis. *Experimental Gerontology, 89*(Supplement C), 30-40. doi:10.1016/j.exger.2016.12.021

Gorus, E., De Raedt, R., Lambert, M., Lemper, J.-C., & Mets, T. (2008). Reaction times and performance variability in normal aging, mild cognitive impairment, and Alzheimer's

disease. *Journal of Geriatric Psychiatry and Neurology, 21*(3), 204-218. doi:10.1177/0891988708320973

Grande, G., Haaksma, M. L., Rizzuto, D., Melis, R. J. F., Marengoni, A., Onder, G., Welmer, A., Fratiglioni, L., & Vetrano, D. L. (2019). Co-occurrence of cognitive impairment and physical frailty, and incidence of dementia: Systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews, 107*, 96-103. doi:10.1016/j.neubiorev.2019.09.001

Greenwood, P. M., & Parasuraman, R. (2010). Neuronal and cognitive plasticity: A neurocognitive framework for ameliorating cognitive aging. *Frontiers in Aging Neuroscience,* 2, 150. doi:10.3389/fnagi.2010.00150

Grimm, K. J., Ram, N., & Estabrook, R. (2016). Growth modeling: Structural equation and multilevel modeling approaches. Guilford Publications.

Gross, A. L., Xue, Q.-L., Bandeen-Roche, K., Fried, L. P., Varadhan, R., McAdams-DeMarco, M. A., Walston, J., & Carlson, M. C. (2016). Declines and impairment in executive function predict onset of physical frailty. *The Journals of Gerontology: Series A, 71*(12), 1624-1630. doi:10.1093/gerona/glw067

Guerreiro, R., & Bras, J. (2015). The age factor in Alzheimer's disease. *Genome Medicine, 7*, 106-106. doi:10.1186/s13073-015-0232-5

Guiney, H., & Machado, L. (2018). Volunteering in the community: Potential benefits for cognitive aging. *The Journals of Gerontology: Series B, 73*(3), 399-408. doi:10.1093/geronb/gbx134

Gunstad, J., Paul, R. H., Cohen, R. A., Tate, D. F., Spitznagel, M. B., & Gordon, E. (2007). Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Comprehensive Psychiatry, 48*(1), 57-61. doi:10.1016/j.comppsych.2006.05.001

Gupta, S. (2018). Impact of volunteering on cognitive decline of the elderly. *The Journal of the Economics of Ageing, 12,* 46-60. doi:10.1016/j.jeoa.2018.01.002

Guralnik, J. M., Ferrucci, L., Pieper, C. F., Leveille, S. G., Markides, K. S., Ostir, G. V., Studenski, S., & Wallace, R. B. (2000). Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *The Journals of Gerontology: Series A, 55*(4), M221-M231. doi:10.1093/gerona/55.4.m221

Hajek, A., Brettschneider, C., Mallon, T., Ernst, A., Mamone, S., Wiese, B., Pentzek, M., Fuchs, A., Stein, J., Luck, T., Bickel, H., Weeg, D., Wagner, M., Heser., K., Maier, W., Scherer, M., Riedel-Heller, S. G., Konig, H-H., & AgeCoDe Study Group. (2017). The impact of social engagement on health-related quality of life and depressive symptoms in old age - evidence from a multicenter prospective cohort study in Germany. *Health and Quality of Life Outcomes, 15*(1), 140-140. doi:10.1186/s12955-017-0715-8

Harada, C. N., Natelson Love, M. C., & Triebel, K. L. (2013). Normal cognitive aging. *Clinics in Geriatric Medicine, 29*(4), 737-752. doi:10.1016/j.cger.2013.07.002

Harris, S. E., & Deary, I. J. (2011). The genetics of cognitive ability and cognitive ageing in healthy older people. *Trends in Cognitive Sciences, 15*(9), 388-394. doi:10.1016/j.tics.2011.07.004

Hassing, L. B. (2018). Light alcohol consumption does not protect cognitive function: A longitudinal prospective study. *Frontiers in Aging Neuroscience, 10*, 81. doi:10.3389/fnagi.2018.00081

Hausdorff, J. M., & Buchman, A. S. (2013). What links gait speed and MCI with dementia? A fresh look at the association between motor and cognitive function. *The Journals of Gerontology: Series A, 68*(4), 409-411. doi:10.1093/gerona/glt002

Hayden, K. M., Reed, B. R., Manly, J. J., Tommet, D., Pietrzak (Pietrzak et al., 2015), R. H., Chelune, G. J., Yang, F. M., Revell, A. J., Bennett, D. A., & Jones, R. N. (2011). Cognitive decline in the elderly: An analysis of population heterogeneity. *Age and Ageing, 40*(6), 684-689. doi:10.1093/ageing/afr101

Hayes, S. M., Alosco, M. L., Hayes, J. P., Cadden, M., Peterson, K. M., Allsup, K., Forman, D. E., Sperling, R. A., & Verfaellie, M. (2015). Physical activity is positively associated with Episodic Memory in aging. *Journal of the International Neuropsychological Society: JINS, 21*(10), 780-790. doi:10.1017/S1355617715000910

He, W., & Larsen, L. J. (2014). *US Census Bureau, American Community Survey Reports, ACS-29, Older Americans with a Disability: 2008–2012*. US Government Printing Office, Washington, DC. https://www.census.gov/library/publications/2014/acs/acs-29.html

Heffernan, M., Andrews, G., Fiatarone Singh, M. A., Valenzuela, M., Anstey, K. J., Maeder, A. J., McNeil, J., Jorm., Lautenschlager, N. T., Sachdev, P. S., Ginige, J.A., Hobbs, M. J., Boulamatsis, C., Chau, T., Cobiac, L., Cox, K. L., Daniel, K., Flood, V. L., Guerrero, Y., … Brodaty, H. (2019). Maintain your brain: Protocol of a 3-year randomized controlled trial of a personalized multi-modal digital health intervention to prevent cognitive decline

among community dwelling 55 to 77 year-olds. *Journal of Alzheimer's Disease, 70*, S221-S237. doi:10.3233/JAD-180572

Hertzog, C. (1985). An individual differences perspective: Implications for cognitive research in gerontology. *Research on Aging, 7*(1), 7-45. doi:10.1177/0164027585007001002

Hertzog, C. (2008). Theoretical approaches to the study of cognitive aging: An individual-differences perspective. In S.M. Hofer & D. F. Alwin (Eds.), *Handbook of cognitive aging: Interdisciplinary perspectives* (pp. 34-49). Thousand Oaks, CA, US: Sage Publications, Inc. doi:10.4135/9781412976589.n2

Hertzog, C., Dixon, R. A., Hultsch, D. F., & MacDonald, S. W. (2003). Latent change models of adult cognition: Are changes in processing speed and working memory associated with changes in episodic memory? *Psychology & Aging, 18*(4), 755-769. doi:10.1037/0882-7974.18.4.755

Hertzog, C., Kramer, A. F., Wilson, R. S., & Lindenberger, U. (2008). Enrichment effects on adult cognitive development: Can the functional capacity of older adults be preserved and enhanced? *Psychological Science in the Public Interest, 9*(1), 1-65. doi:10.1111/j.1539-6053.2009.01034.x

Hicks, M. M., & Conner, N. E. (2014). Resilient ageing: A concept analysis. *Journal of Advanced Nursing, 70*(4), 744-755. doi:10.1111/jan.12226

Hofer, S. M., & Piccinin, A. M. (2010). Toward an integrative science of life-span development and aging. *The Journals of Gerontology: Series B, 65B*(3), 269-278. doi:10.1093/geronb/gbq017

Hohman, T. J., Tommet, D., Marks, S., Contreras, J., Jones, R., & Mungas, D. (2017). Evaluating Alzheimer's disease biomarkers as mediators of age-related cognitive decline. *Neurobiology of Aging, 58*, 120-128. doi:10.1016/j.neurobiolaging.2017.06.022

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: a meta-analytic review. *PLoS medicine, 7*(7), e1000316-e1000316. doi:10.1371/journal.pmed.1000316

Hong, Z., Ng, K. K., Sim, S. K. Y., Ngeow, M. Y., Zheng, H., Lo, J. C., Chee, M. W. L., & Zhou, J. (2015). Differential age-dependent associations of gray matter volume and white matter integrity with processing speed in healthy older adults. *NeuroImage, 123*, 42-50. doi:10.1016/j.neuroimage.2015.08.034

Hoogendam, Y. Y., Hofman, A., van der Geest, J. N., van der Lugt, A., & Ikram, M. A. (2014). Patterns of cognitive function in aging: The Rotterdam Study. *European Journal of Epidemiology, 29*(2), 133-140. doi:10.1007/s10654-014-9885-4

Hoogendijk, E. O., Rijnhart, J. J. M., Skoog, J., Robitaille, A., van den Hout, A., Ferrucci, L., Huisman, M., Skoog, I., Piccinin, A., Hofer, S. M., & Muniz Terrera, G. (2020). Gait speed as predictor of transition into cognitive impairment: Findings from three longitudinal studies on aging. *Experimental Gerontology, 129,* 110783. doi:10.1016/j.exger.2019.110783

Hoogendijk, E. O., Suanet, B., Dent, E., Deeg, D. J. H., & Aartsen, M. J. (2016). Adverse effects of frailty on social functioning in older adults: Results from the Longitudinal Aging Study Amsterdam. *Maturitas, 83*, 45-50. doi:10.1016/j.maturitas.2015.09.002

Hoogendijk, E. O., Theou, O., Rockwood, K., Onwuteaka-Philipsen, B. D., Deeg, D. J. H., & Huisman, M. (2017). Development and validation of a frailty index in the Longitudinal

Aging Study Amsterdam. *Aging Clinical and Experimental Research, 29*(5), 927-933. doi:10.1007/s40520-016-0689-0

Hoover, M., Rotermann, M., Sanmartin, C., & Bernier, J. (2013). Validation of an index to estimate the prevalence of frailty among community-dwelling seniors. *Health Reports, 24(*9), 10-17.

Hughes, T. M., Kuller, L. H., Barinas-Mitchell, E. J., Mackey, R. H., McDade, E. M., Klunk, W. E., Aizenstein, H. J., Cohen, A. D., Snitz, B. E., Mathis, C. A., Dekosky, S. T., & Lopez, O. L. (2013). Pulse wave velocity is associated with β-amyloid deposition in the brains of very elderly adults. *Neurology, 81*(19), 1711–1718. doi:10.1212/01.wnl.0000435301.64776.37

Huisingh-Scheetz, M., Wroblewski, K., Kocherginsky, M., Huang, E., Dale, W., Waite, L., & Schumm, L. P. (2018). The relationship between physical activity and frailty among U.S. older adults based on hourly accelerometry data. *Journal of Gerontology: Series A, 73*(5), 622-629. doi:10.1093/gerona/glx208

Hultsch, D. F., Hertzog, C., Small, B. J., & Dixon, R. A. (1999). Use it or lose it: Engaged lifestyle as a buffer of cognitive decline in aging? *Psychology of Aging, 14*(2), 245. doi:10.1037/0882-7974.14.2.245

Hyer, L., Scott, C., Atkinson, M. M., Mullen, C. M., Lee, A., Johnson, A., & McKenzie, L. C. (2016). Cognitive training program to improve working memory in older adults with MCI. *Clinical gerontologist, 39*(5), 410-427. doi:10.1080/07317115.2015.1120257

Idler, E. L., & Benyamini, Y. (1997). Self-rated health and mortality: A review of twenty-seven community studies. *Journal of Health and Social Behavior*, 21-37.

Infurna, F. J., Okun, M. A., & Grimm, K. J. (2016). Volunteering is associated with lower risk of cognitive impairment. *Journal of the American Geriatrics Society, 64*(11), 2263-2269. doi:10.1111/jgs.14398

Inglés, M., Gambini, J., Mas-Bargues, C., García-García, F. J., Viña, J., & Borrás, C. (2016). Brain-Derived Neurotrophic Factor as a marker of cognitive frailty. *The Journals of Gerontology: Series A, 72(*3), 450-451. doi:10.1093/gerona/glw145

Institute of Medicine. (2015). *Cognitive aging: Progress in understanding and opportunities for action.* Washington, DC: The National Academies Press. doi:10.17226-21693

Isaacson, R. S., Ganzer, C. A., Hristov, H., Hackett, K., Caesar, E., Cohen, R., Kachko, R., Melendez-Caberero, J., Rahman, A., Scheyer, O., Hwang, M. J., Berkowitz, C., Hendrix, S., Mureb, M., Schelke, M. W., Mosconi, L., Seifan, A., & Krikorian, R. (2018). The clinical practice of risk reduction for Alzheimer's disease: A precision medicine approach. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 14*(12), 1663-1673. doi:10.1016/j.jalz.2018.08.004

Jansen, W. J., Wilson, R. S., Visser, P. J., Nag, S., Schneider, J. A., James, B. D., Leurgans, S. E., Capuano, A.W., Bennet, D. A., & Boyle, P. A. (2018). Age and the association of dementia-related pathology with trajectories of cognitive decline. *Neurobiology of Aging, 61*, 138-145. doi:10.1016/j.neurobiolaging.2017.08.029

Jensen, C. S., Simonsen, A. H., Siersma, V., Beyer, N., Frederiksen, K. S., Gottrup, H., Hoffman, K., Høgh, P., Frikke-Schmidt, R., Sobol, N. A., Waldemar, G., Wermuth, L., & Hasselbalch, S. G. (2019). Patients with Alzheimer's disease who carry the APOE ε4 allele benefit more from physical exercise. *Alzheimer's & Dementia: Translational Research & Clinical Interventions, 5*, 99-106. doi:10.1016/j.trci.2019.02.007

Jin, K., Simpkins, J. W., Ji, X., Leis, M., & Stambler, I. (2015). The critical need to promote research of aging and aging-related diseases to improve health and longevity of the elderly population. *Aging and Disease, 6*(1), 1-5. doi:10.14336/ad.2014.1210

Josefsson, M., de Luna, X., Pudas, S., Nilsson, L. G., & Nyberg, L. (2012). Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. *Journal of the American Geriatric Society, 60*(12), 2308-2312. doi:10.1111/jgs.12000

Jung, T., & Wickrama, K. A. (2008). An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Psychology Compass, 2*(1), 302-317. doi:10.1111/j.1751-9004.2007.00054.x

Karatsoreos, I. N., & McEwen, B. S. (2013). Resilience and vulnerability: A neurobiological perspective. *F1000Prime Reports, 5*, 13-13. doi:10.12703/P5-13

Kaup, A. R., Byers, A. L., Falvey, C., Simonsick, E. M., Satterfield, S., Ayonayon, H. N., Smagula, S. F., Rubin, S. M., & Yaffe, K. (2016). Trajectories of depressive symptoms in older adults and risk of dementia. *Journal of American Medical Association Psychiatry, 73*(5), 525-531. doi:10.1001/jamapsychiatry.2016.0004

Kaup, A. R., Nettiksimmons, J., Harris, T. B., Sink, K. M., Satterfield, S., Metti, A. L., Ayonayon, H. A., & Yaffe, K. (2015). Cognitive resilience to apolipoprotein E ε4: Contributing factors in black and white older adults. *Journal of the American Medical Association Neurology, 72*(3), 340-348. doi:10.1001/jamaneurol.2014.3978

Kharicha, K., Iliffe, S., Harari, D., Swift, C., Gillmann, G., & Stuck, A. E. (2007). Health risk appraisal in older people: Are older people living alone an ‘at-risk’ group? *British Journal of General Practice, 57*(537), 271. doi:10.1002/central/CN-00587613

Kikkert, L. H. J., Vuillerme, N., van Campen, J. P., Hortobágyi, T., & Lamoth, C. J. (2016). Walking ability to predict future cognitive decline in old adults: A scoping review. *Ageing Research Reviews, 27,* 1-14. doi:10.1016/j.arr.2016.02.001

Kivipelto, M., Mangialasche, F., & Ngandu, T. (2018). Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nature Reviews Neurology, 14*(11), 653-666. doi:10.1038/s41582-018-0070-3

Klaming, R., Annese, J., Veltman, D. J., & Comijs, H. C. (2017). Episodic memory function is affected by lifestyle factors: a 14-year follow-up study in an elderly population. *Aging, Neuropsychology, and Cognition, 24(*5), 528-542. doi:10.1080/13825585.2016.1226746

Knight, S., & Edwards, V. (2008). In the company of wolves: The physical, social, and psychological benefits of dog qwnership. *Journal of Aging and Health, 20*(4), 437-455. doi:10.1177/0898264308315875

Koch, M., Fitzpatrick, A. L., Rapp, S. R., Nahin, R. L., Williamson, J. D., Lopez, O. L., DeKosky, S. T., Kuller, L. H., Mackey, R. H., Mukamal, K. J., Jensen, M. K., & Sink, K. M. (2019). Alcohol consumption and risk of dementia and cognitive decline among older adults with or without mild cognitive impairment. *Journal of the American Medical Association Network Open, 2*(9), e1910319-e1910319. doi:10.1001/jamanetworkopen.2019.10319

Kojima, G., Iliffe, S., & Walters, K. (2017). Frailty index as a predictor of mortality: A systematic review and meta-analysis. *Age and Ageing, 47*(2), 193-200. doi:10.1093/ageing/afx162

Kojima, G., Taniguchi, Y., Iliffe, S., & Walters, K. (2016). Frailty as a predictor of Alzheimer disease, vascular dementia, and all dementia among community-dwelling older people: A

systematic review and meta-analysis. *Journal of the American Medical Directors Association, 17*(10), 881-888. doi:10.1016/j.jamda.2016.05.013

Kok, R. M., & Reynolds, C. F., III. (2017). Management of depression in older adults: A review. *Journal of the American Medical Association, 317*(20), 2114-2122. doi:10.1001/jama.2017.5706

Kotwal, A. A., Kim, J., Waite, L., & Dale, W. (2016). Social function and cognitive status: Results from a US nationally representative survey of older adults. *Journal of General Internal Medicine, 31*(8), 854-862. doi:10.1007/s11606-016-3696-0

Kuate-Tegueu, C., Avila-Funes, J.-A., Simo, N., Le Goff, M., Amieva, H., Dartigues, J.-F., & Tabue-Teguo, M. (2017). Association of gait speed, psychomotor speed, and dementia. *Journal of Alzheimer's Disease, 60(*2), 585-592. doi:10.3233/JAD/170267

Kuiper, J. S., Zuidersma, M., Oude Voshaar, R. C., Zuidema, S. U., van den Heuvel, E. R., Stolk, R. P., & Smidt, N. (2015). Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Reviews, 22*, 39-57. doi:10.1016/j.arr.2015.04.006

Lahiri, D. K., Sambamurti, K., & Bennett, D. A. (2004). Apolipoprotein gene and its interaction with the environmentally driven risk factors: molecular, genetic and epidemiological studies of Alzheimer’s disease. *Neurobiology of Aging, 25*(5), 651-660. doi:10.1016/j.neurobiolaging.2003.12.024

Lampit, A., Valenzuela, M., & Gates, N. J. (2015). Computerized cognitive training is beneficial for older adults. *Journal of the American Geriatrics Society, 63*(12), 2610-2612. doi:10.1371/journal.pone.0040588

Landi, F., Abbatecola, A. M., Provinciali, M., Corsonello, A., Bustacchini, S., Manigrasso, L., Cherubini, A., Bernabei, R., & Lattanzio, F. (2010). Moving against frailty: Does physical activity matter? *Biogerontology, 11*(5), 537-545. doi:10.1007/s10522-010-9296-1

Langa K. M. (2015). Is the risk of Alzheimer's disease and dementia declining? *Alzheimer's Research & Therapy, 7(*1), 34. doi:10.1186/s13195-015-0118-1

Langlois, F., Vu, T. T. M., Kergoat, M.-J., Chassé, K., Dupuis, G., & Bherer, L. (2012). The multiple dimensions of frailty: Physical capacity, cognition, and quality of life. *International Psychogeriatrics, 24*(9), 1429-1436. doi:10.1017/S1041610212000634

Lansbury, L. N., Roberts, H. C., Clift, E., Herklots, A., Robinson, N., & Sayer, A. A. (2017). Use of the electronic Frailty Index to identify vulnerable patients: A pilot study in primary care. *British Journal of General Practice, 67*(664), e751-756. doi:10.3399/bjgp17x693089

Lau, H., Mat Ludin, A. F., Rajab, N. F., & Shahar, S. (2017). Identification of neuroprotective factors associated with successful ageing and risk of cognitive impairment among Malaysia older adults. *Current Gerontology and Geriatrics Research, 2017*, 7. doi:10.1155/2017/4218756

Laukka, E. J., Lovden, M., Herlitz, A., Karlsson, S., Ferencz, B., Pantzar, A., Keller, L., Graff, C., Fratiglionli, L., & Backman, L. (2013). Genetic effects on old-age cognitive functioning: A population-based study. *Psychology & Aging, 28*. (1), 262-274. doi:10.1037/a0030829

Lavretsky, H. (2014). *Resilience and aging: Research and practice.* Baltimore, MD, John Hopkins University Press.

Laws, K. R., Irvine, K., & Gale, T. M. (2016). Sex differences in cognitive impairment in Alzheimer's disease. *World Journal of Psychiatry, 6*(1), 54-65. doi:10.5498/wjp.v6.i1.54

Lee, H. J., Seo, H. I., Cha, H. Y., Yang, Y. J., Kwon, S. H., & Yang, S. J. (2018). Diabetes and Alzheimer's disease: Mechanisms and nutritional aspects. *Clinical Nutrition Research, 7*(4), 229-240. doi:10.7762/cnr.2018.7.4.229.

Lenehan, M. E., Summers, M. J., Saunders, N. L., Summers, J. J., & Vickers, J. C. (2015). Relationship between education and age-related cognitive decline: A review of recent research. *Psychogeriatrics, 15*(2), 154-162. doi:10.1111/psyg.12083

Levin, R. A., Carnegie, M. H., & Celermajer, D. S. (2020). Pulse pressure: An emerging therapeutic target for dementia. *Frontiers in Neuroscience, 14*, 669. doi:10.3389/fnins.2020.00669

Lezak, M. D. (1983). *Neuropsychological assessment*. New York, NY: Oxford University Press.

Li, K. Z. H., Vadaga, K. K., Bruce, H., & Lai, L. (2017). Executive function development in aging. *Executive Function: Development Across the Life Span*, 59-72. doi:10.4324/9781315160719-5

Li, X., Lyu, P., Ren, Y., An, J., & Dong, Y. (2017). Arterial stiffness and cognitive impairment. *Journal of the Neurological Sciences,* 380, 1-10. doi:10.1016/j.jns.2017.06.018

Lista, I., & Sorrentino, G. (2010). Biological mechanisms of physical activity in preventing cognitive decline. *Cellular and Molecular Neurobiology, 30*(4), 493-503. doi:10.1007/s10571-009-9488-x

Liu, H., Zhang, Y., Burgard, S. A., & Needham, B. L. (2019). Marital status and cognitive impairment in the United States: Evidence from the National Health and Aging Trends Study. *Annals of Epidemiology, 38,* 28-34. doi:10.1016/j.annepidem.2019.08.007

Liu, H., Zhang, Z., Choi, S.-W., & Langa, K. M. (2020). Marital status and dementia: Evidence from the health and retirement study. *The Journals of Gerontology: Series B, 75*(8), 1783-1795. doi:10.1093/geronb/gbz087

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costagreda, S., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson., E. B., … & Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet, 390*(10113), 2673-2734. doi:10.1016/S0140-6736(20)30367-6

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., . . . & Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet, 396*(10248), 413-446. doi:10.1016/S0140-6736(20)30367-6

Loprinzi, P. D., & Frith, E. (2018). Obesity and episodic memory function. *The Journal of Physiological Sciences, 68*(4), 321-331. doi:10.1007/s12576-018-0612-x

Lourida, I., Hannon, E., Littlejohns, T. J., Langa, K. M., Hyppönen, E., Kuźma, E., & Llewellyn, D. J. (2019). Association of lifestyle and genetic risk with incidence of dementia. *Journal of the American Medical Association, 322*(5), 430-437. doi:10.1001/jama.2019.9879

Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S., & Schmiedek, F. (2010). A theoretical framework for the study of adult cognitive plasticity. *Psychological Bulletin, 136*(4), 659. doi:10.1037/a0020080

Lu, P. H., Lee, G. J., Raven, E. P., Tingus, K., Khoo, T., Thompson, P. M., & Bartzokis, G. (2011). Age-related slowing in cognitive processing speed is associated with myelin integrity in a very healthy elderly sample. *Journal of Clinical and Experimental Neuropsychology, 33*(10), 1059-1068. doi:10.1080/13803395.2011.595397

Lu, P. H., Lee, G. J., Tishler, T. A., Meghpara, M., Thompson, P. M., & Bartzokis, G. (2013). Myelin breakdown mediates age-related slowing in cognitive processing speed in healthy elderly men. *Brain and Cognition, 81*(1), 131-138. doi:10.1016/j.bandc.2012.09.006

Luszcz, M. (Ed.) (2011). *Executive function and cognitive aging* (Vol. 7). San Diego, CA: Academic Press.

MacDonald, S. W. S., Hundza, S., Love, J. A., DeCarlo, C. A., Halliday, D. W. R., Brewster, P. W. H., Lukyn, T. V., Camicioli, R., & Dixon, R. A. (2017). Concurrent indicators of gait velocity and variability are associated with 25-year cognitive change: A retrospective longitudinal investigation. *Frontiers of Aging Neuroscience, 9*(17). doi:10.3389/fnagi.2017.00017

MacLeod, S., Musich, S., Hawkins, K., Alsgaard, K., & Wicker, E. R. (2016). The impact of resilience among older adults. *Geriatric Nursing, 37*(4), 266-272. doi:10.1016/j.gerinurse.2016.02.014

Makar, T. K., Trisler, D., Sura, K. T., Sultana, S., Patel, N., & Bever, C. T. (2008). Brain derived neurotrophic factor treatment reduces inflammation and apoptosis in experimental allergic encephalomyelitis. *Journal of the Neurological Sciences, 270*(1-2), 70-76. doi:10.1016/j.jns.2008.02.001

Mankovsky, B., Zherdova, N., van den Berg, E., Biessels, G. J., & de Bresser, J. (2018). Cognitive functioning and structural brain abnormalities in people with Type 2 diabetes mellitus. *Diabetic Medicine, 35*(12), 1663-1670. doi:10.1111/dme.13800

Mänty, M., Heinonen, A., Viljanen, A., Pajala, S., Koskenvuo, M., Kaprio, J., & Rantanen, T. (2010). Self-reported preclinical mobility limitation and fall history as predictors of future falls in older women: Prospective cohort study. *Osteoporosis International, 21*(4), 689-693. doi:10.1007/s00198-009-0950-x

Marioni, R. E., Proust-Lima, C., Amieva, H., Brayne, C., Matthews, F. E., Dartigues, J.-F., & Jacqmin-Gadda, H. (2015). Social activity, cognitive decline and dementia risk: A 20-year prospective cohort study. *BMC Public Health, 15*(1), 1089. doi:10.1186/s12889-015-2426-6

Marseglia, A., Dahl Aslan, A. K., Fratiglioni, L., Santoni, G., Pedersen, N. L., & Xu, W. (2017). Cognitive trajectories of older adults with prediabetes and diabetes: A population-based cohort study. *The Journals of Gerontology: Series A, 73*(3), 400-406. doi:10.1093/gerona/glx112

Martinowich, K., Manji, H., & Lu, B. (2007). New insights into BDNF function in depression and anxiety. *Nature Neuroscience, 10*(9), 1089-1093. doi:10.1038/nn1971

Marusic, U., Verghese, J., & Mahoney, J. R. (2018). Cognitive-based interventions to improve mobility: A systematic review and meta-analysis. *Journal of the American Medical Directors Association, 19*(6), 484-491. doi:10.1016/j.jamda.2018.02.002

Masters, C. L., Bateman, R., Blennow, K., Rowe, C. C., Sperling, R. A., & Cummings, J. L. (2015). Alzheimer's disease. *Nature Reviews Neurology, 1*, 15056-15056. doi:10.1038/nrdp.2015.56

Matchock, R. L. (2015). Pet ownership and physical health. *Current Opinion in Psychiatry, 28*(5), 386-392. doi:10.1097/yco.0000000000000183

McCarrey, A. C., An, Y., Kitner-Triolo, M. H., Ferrucci, L., & Resnick, S. M. (2016). Sex differences in cognitive trajectories in clinically normal older adults. *Psychology of Aging, 31*(2), 166-175. doi:10.1037/pag0000070

McDade, E., Sun, Z., Lee, C.-W., Snitz, B., Hughes, T., Chang, C.-C. H., & Ganguli, M. (2016). The association between pulse pressure change and cognition in late life: Age and where you start matters. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 4,* 56-66. doi:10.1016/j.dadm.2016.03.008

McDermott, K. L., McFall, G. P., Andrews, S. J., Anstey, K. J., & Dixon, R. A. (2017). Memory resilience to Alzheimer's genetic risk: Sex effects in predictor profiles. *The Journals of Gerontology: Series B, 72*(6), 937-946. doi:10.1093/geronb/gbw161

McFall, G. P., McDermott, K. L., & Dixon, R. A. (2019). Modifiable risk factors discriminate memory trajectories in non-demented aging: Precision factors and targets for promoting healthier brain aging and preventing dementia. *Journal of Alzheimer's Disease, 70*, S101-S118. doi:10.3233/JAD-180571

McFall, G. P., Wiebe, S. A., Vergote, D., Anstey, K. J., & Dixon, R. A. (2015). Alzheimer's genetic risk intensifies neurocognitive slowing associated with diabetes in nondemented older adults. *Alzheimer's and Dementia,* 1(4), 395-402. doi:10.1016/j.dadm.2015.08.002

McFall, G. P., Wiebe, S. A., Vergote, D., Jhamandas, J., Westaway, D., & Dixon, R. A. (2014). IDE (rs6583817) polymorphism and pulse pressure are independently and interactively associated with level and change in executive function in older adults. *Psychology of Aging, 29(*2), 418-430. doi:10.1037/a0034656

McFall, G. P., Wiebe, S. A., Vergote, D., Westaway, D., Jhamandas, J., & Dixon, R. A. (2013). IDE (rs6583817) polymorphism and type 2 diabetes differentially modify executive function in older adults. *Neurobiology of Aging, 34*(9), 2208-2216. doi:10.1016/j.neurobiolaging.2013.03.010

McFall, G. P., Wiebe, S. A., Vergote, D., Westaway, D., Jhamandas, J., Bäckman, L., & Dixon, R. A. (2015). *APOE* and pulse pressure interactively influence level and change in the aging of episodic memory: Protective effects among ε2 carriers. *Neuropsychology, 29*(3), 388-401. doi:10.1037/neu0000150

McGough, E. L., Kelly, V. E., Logsdon, R. G., McCurry, S. M., Cochrane, B. B., Engel, J. M., & Teri, L. (2011). Associations between physical performance and executive function in older adults with Mild Cognitive Impairment: Gait speed and the Timed "Up & Go" Test. *Physical Therapy, 91*(8), 1198-1207. doi:10.2522/ptj.20100372

McGrath, R., Vincent, B. M., Hackney, K. J., Robinson-Lane, S. G., Downer, B., & Clark, B. C. (2020). The longitudinal associations of handgrip strength and cognitive function in aging Americans. *Journal of the American Medical Directors Association, 21(*5), 634-639.e631. doi:10.1016/j.jamda.2019.08.032

Melzer, D., Dik, M. G., van Kamp, G. J., Jonker, C., Deeg, D. J. (2005). The apolipoprotein E e4 polymorphism is strongly associated with poor mobility performance test results but not self-reported limitations in older people. *Journal of Gerontology: Series A, 60*(10), 1319-1323. doi:10.1093/Gerona/60.10.1319

Meng, X., & D'Arcy, C. (2012). Education and dementia in the context of the cognitive reserve hypothesis: A systematic review with meta-analyses and qualitative analyses. *PLoS One, 7*(6), e38268. doi:10.1371/journal.pone.0038268

Middleton, L., Barnes, D., Lui, L., & Yaffe, K. (2010). Physical activity over the life course and its association with cognitive performance and impairment in old age. *Journal of the American Geriatric Soceity., 58,* 1322-1326. doi:10.1111/j.1532-5415.2010.02903.x

Mitnitski, A. B., Graham, J. E., Mogilner, A. J., & Rockwood, K. (2002). Frailty, fitness and late-life mortality in relation to chronological and biological age. *BMC Geriatrics, 2*, 1-1. doi:10.1186/1471-2318-2-1

Mitnitski, A. B., Mogilner, A. J., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *Scientific World Journal, 1*, 323-36. doi:10.1100/tsw.2001.58

Mitnitski, A., Fallah, N., Rockwood, M. R., & Rockwood, K. (2011). Transitions in cognitive status in relation to frailty in older adults: A comparison of three frailty measures. *The Journal of Nutrition, Health & Aging, 15*(10), 863-867. doi:10.1007/s12603-011-0066-9

Mitnitski, A., Song, X., & Rockwood, K. (2007). Improvement and decline in health status from late middle age: Modeling age-related changes in deficit accumulation. *Experimental Gerontology, 42,* 1109-15. doi:10.1016/j.exger.2007.08.002

Montero-Odasso, M., Bherer, L., Studenski, S., Gopaul, K., Oteng-Amoako, A., Woolmore-Goodwin, S., Stolle, P., Wells, J., Doherty, T., Zecevic, A. A., Galinsky, D., Rylett, R. J., Jutai, J., Muir-Hunter, S., Speechley, M., & Camicioli, R. (2015). Mobility and cognition in seniors. Report from the 2008 Institute of Aging (CIHR) Mobility and Cognition Workshop. *Canadian Geriatrics Journal, 18*(3), 159-167. doi:10.5770/cgj.18.188

Montero-Odasso, M., Verghese, J., Beauchet, O., & Hausdorff, J. M. (2012). Gait and cognition: A complementary approach to understanding brain function and the risk of falling. *Journal of the American Geriatrics Society, 60*(11), 2127-2136. doi:10.1111/j.1532-5415.2012.04209.x

Montine, T. J., Cholerton, B. A., Corrada, M. M., Edland, S. D., Flanagan, M. E., Hemmy, L. S., Kawas, C. H., & White, L. R. (2019). Concepts for brain aging: resistance, resilience, reserve, and compensation. *Alzheimer's Research & Therapy, 11*(1), 1-3. doi:10.1186/s13195-019-0479-y

Moran, C., Phan, T. G., Chen, J., Blizzard, L., Beare, R., Venn, A., Wood, A. G., Forbes, J., Greenaway, T. M., Pearson, S., & Srikanth, V. (2013). Brain atrophy in type 2 diabetes: Regional distribution and influence on cognition. *Diabetes Care, 36*(12), 4036-4042. doi:10.2337/dc13-0143

Moretti, F., De Ronchi, D., Bernabei, V., Marchetti, L., Ferrari, B., Forlani, C., Negretti, F., Sacchetti, C., & Atti, A. R. (2011). Pet therapy in elderly patients with mental illness. *Psychogeriatrics: The Official Journal of the Japanese Psychogeriatric Society, 11*(2), 125-129. doi:10.1111/j.1479-8301.2010.00329.x

Morris, L. J., D'Este, C., Sargent-Cox, K., & Anstey, K. J. (2016). Concurrent lifestyle risk factors: Clusters and determinants in an Australian sample. *Preventative Medicine, 84*, 1-5. doi:10.1016/j.ypmed.2015.12.009

Mortamais, M., Ash, J. A., Harrison, J., Kaye, J., Kramer, J., Randolph, C., Pose, C., Albala, B., Ropacki, M., Ritchie, C. W., & Ritchie, K. (2017). Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility. *Alzheimer's & Dementia, 13*(4), 468-492. doi:10.1016/j.jalz.2016.06.2365

Mousavi-Nasab, S. M. H., Kormi-Nouri, R., Sundström, A., & Nilsson, L.-G. (2012). The effects of marital status on episodic and semantic memory in healthy middle-aged and old individuals. *Scandinavian Journal of Psychology, 53*(1), 1-8. doi:10.1111/j.1467-9450.2011.00926.x

Mungas, D., Gavett, B., Fletcher, E., Farias, S. T., DeCarli, C., & Reed, B. (2018). Education amplifies brain atrophy effect on cognitive decline: implications for cognitive reserve. *Neurobiology of Aging, 68*, 142-150. doi:10.1016/j.neurobiolaging.2018.04.002

Munro, C. A., Winicki, J. M., Schretlen, D. J., Gower, E. W., Turano, K. A., Muñoz, B., Keay, L., Bandeen-Roche, K., & West, S. K. (2012). Sex differences in cognition in healthy elderly individuals. *Aging, Neuropsychology, and Cognition, 19*(6), 759-768. doi:10.1080/13825585.2012.690366

Muscedere, J., Andrew, M. K., Bagshaw, S. M., Estabrooks, C., Hogan, D., Holroyd-Leduc, J., Howeltt, S., Lahey, W., Maxwell, C., McNally, M., Moorhouse, P., Rockwood, K., Rolfson, D., Sinah, S., Tholl, B., & Canadian Frailty Network. (2016). Screening for frailty in Canada's health care system: A time for action. *Canadian Journal on Aging/La Revue Canadienne du Vieillissement, 35*(3), 281-297. doi:10.1017/S0714980816000301

Muthén, L., & Muthén, B. (1998). Mplus User's Guide (7th edn). Muthén & Muthén: Los Angeles, CA, USA, 2012.

Nagai, M., Hoshide, S., & Kario, K. J. A. (2010). Hypertension and dementia. *American Journal of Hypertension, 23*(2), 116-124. doi:10.1038/ajh.2009.212

Nation, D. A., Preis, S. R., Beiser, A., Bangen, K. J., Delano-Wood, L., Lamar, M., Libon, D. J., Seshadri, S., Wolf, P. A., & Au, R. (2016). Pulse pressure is associated with early brain atrophy and cognitive decline: Modifying effects of APOE-ε4. *Alzheimer Disease and Associated Disorders, 30(*3), 210–215. doi:10.1097/WAD.0000000000000127

National Research Council. (2011). *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease.* Washington, DC: National Academies Press.

Navarro-Martínez, R., Fernández-Garrido, J., Buigues, C., Torralba-Martínez, E., Martinez-Martinez, M., Verdejo, Y., Mascarós, M. C., & Cauli, O. (2015). Brain-derived neurotrophic factor correlates with functional and cognitive impairment in non-disabled older individuals. *Experimental Gerontology, 72*, 129-137. doi:10.1016/j.exger.2015.10.001

Neafsey, E. J., & Collins, M. A. (2011). Moderate alcohol consumption and cognitive risk. *Neuropsychiatric Disease and Treatment, 7*, 465-484. doi:10.2147/NDT.S23159

Negash, S., Wilson, R., Leurgans, S., Wolk, D., Schneider, J., Buchman, A., Bennet, D. A., & Arnold, S. (2013). Resilient brain aging: Characterization of discordance between Alzheimer's disease pathology and cognition. *Current Alzheimer Research, 10*(8), 844-851. doi:10.2174/15672050113109990157

Negash, S., Xie, S., Davatzikos, C., Clark, C. M., Trojanowski, J. Q., Shaw, L. M., Wolk, D. A., & Arnold, S. E. (2013). Cognitive and functional resilience despite molecular evidence of Alzheimer's disease pathology. *Alzheimer's and Dementia, 9*(3), e89-95. doi:10.1016/j.jalz.2012.01.009

Neumann, S., Kwisda, S., Krettek, C., & Gaulke, R. (2017). Comparison of the grip strength using the Martin-Vigorimeter and the JAMAR-dynamometer: Establishment of normal values. *In Vivo, 31*(5), 917-924, doi:10.21873/invivo.11147

Nevado-Holgado, A. J., Kim, C.-H., Winchester, L., Gallacher, J., & Lovestone, S. (2016). Commonly prescribed drugs associate with cognitive function: A cross-sectional study in UK Biobank. *BMJ Open, 6*(11), e012177. doi:10.1136/bmjopen-2016-012177

Newman, A. B., Simonsick, E. M., Naydeck, B. L., Boudreau, R. M., Kritchevsky, S. B., Nevitt, M. C., Pahor, M., Satterfield, S., Brach, J. S., Studenski, A. S., & Harris, T. B. (2006).

Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *Journal of the American Medical Association, 295*(17), 2018-2026. doi:10.1001/jama.295.17.2018

Ng, T. P., Feng, L., Nyunt, M. S. Z., Feng, L., Niti, M., Tan, B. Y., Chan, G., Khoo, S. A., Chan, S. M., Yap, P., & Yap, B. Y. (2015). Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: A randomized controlled trial. *The American Journal of Medicine, 128*(11), 1225-1236. doi:10.1016/j.amjmed.2015.06.017

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., Backman, L., Hanninen, T., Jula, A., Laatikainen, T., Lindstrom, J., Mangialasche, F., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Standberg, . . . & Kivipelto, M. (2015). A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *The Lancet, 385*(9984), 2255-2263. doi:10.1016/S0140-6736(15)60461-5

Nucci, M., Mapelli, D., & Mondini, S. (2012). Cognitive Reserve Index questionnaire (CRIq): A new instrument for measuring cognitive reserve. *Aging Clinical and Experimental Research, 24*(3), 218-226. doi:10.3275/7800

Nyberg, L. (2017). Functional brain imaging of episodic memory decline in ageing. *Journal of Internal Medicine, 281*(1), 65-74. doi:10.1111/joim.12533

Nyberg, L., Bäckman, L., Erngrund, K., Olofsson, U., & Nilsson, L.-G. (1996). Age differences in episodic memory, semantic memory, and priming: Relationships to demographic, intellectual, and biological factors. *The Journals of Gerontology: Series B, 51*(4), P234-P240. doi:10.1093/geronb/51B.4.P234

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences, 16*(5), 292-305. doi:10.1016/j.tics.2012.04.005

Nylund, K. L., Asparouhob, T., & Muthén, B. O. (2007). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Structural Equation Modeling, 14(*4), 535-569. doi:10.1080/10705510701575396

Nyström, M. B. T., Sörman, D. E., Kormi-Nouri, R., & Rönnlund, M. (2019). To what extent is subjective well-being in late adulthood related to subjective and objective memory functioning? Five-year cross-lagged panel analyses. *Aging & Mental Health, 23*(1), 92–99. doi:10.1080/13607863.2017.1394439

O'Donoghue, M. C., Murphy, S. E., Zamboni, G., Nobre, A. C., & Mackay, C. E. (2018). APOE genotype and cognition in healthy individuals at risk of Alzheimer's disease: A review. *Cortex, 104*, 103-123. doi:10.1016/j.cortex.2018.03.025

Ojagbemi, A., D'Este, C., Verdes, E., Chatterji, S., & Gureje, O. (2015). Gait speed and cognitive decline over 2 years in the Ibadan study of aging. *Gait & Posture, 41*(2), 736-740. doi:10.1016/j.gaitpost.2015.01.011

Okonkwo, O. C., & Vemuri, P. (2017). Stemming the Alzheimer tsunami: Introduction to the special issue on reserve and resilience in Alzheimer's disease. *Brain Imaging and Behavior, 11*(2), 301-303. doi:10.1007/s11682-017-9677-z

Okoro C. A., Hollis N. D., Cyrus A. C., & Griffin-Blake S. (2018). Prevalence of disabilities and health care access by disability status and type among adults — United States, 2016. *MMWR Morbidity and Mortality Weekly Report, 67*, 882–887. doi:10.15585/mmwr.mm6732a3external icon

Okusaga, O., Stewart, M. C. W., Butcher, I., Deary, I., Fowkes, F. G. R., & Price, J. F. (2013). Smoking, hypercholesterolaemia and hypertension as risk factors for cognitive impairment in older adults. *Age and Ageing, 42*(3), 306-311. doi:10.1093/ageing/afs193

Olaya, B., Bobak, M., Haro, J. M., & Demakakos, P. (2017). Trajectories of verbal episodic memory in middle-aged and older adults: Evidence from the English Longitudinal Study of Ageing. *Journal of the American Geriatrics Society, 65*(6), 1274-1281. doi:10.1111/jgs.14789

Opdebeeck, C., Martyr, A., & Clare, L. (2016). Cognitive reserve and cognitive function in healthy older people: A meta-analysis. *Aging, Neuropsychology, and Cognition, 23*(1), 40-60. doi:10.1080/13825585.2015.1041450

Ott, A., Slooter, A., Hofman, A., van Harskamp, F., Witteman, J., Van Broeckhoven, C., van Duijn, C. M., & Breteler, M. M. (1998). Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: The Rotterdam Study. *The Lancet, 351*(9119), 1840-1843. doi:10.1016/s0140-6736(97)07541-7

Palmer, J., MacLeod, C. M., Hunt, E., & Davidson, J. E. (1985). Information processing correlates of reading. *Journal of Memory and Language, 24*, 59–88. doi:10.1016/0749-596X(85)90016-6

Palta, P., Carlson, M. C., Crum, R. M., Colantuoni, E., Sharrett, A. R., Yasar, S., Nahin, R. L., DeKosky, S. T., Snitz, B., Lopez, O., Williamson, J. D., Furberg, C. D., Rapp, S. R., & Golden, S. H. (2017). Diabetes and cognitive decline in older adults: The ginkgo evaluation of memory study. *The Journals of Gerontology: Series A, 73*(1), 123-130. doi:10.1093/gerona/glx076

Papp, K. V., Kaplan, R. F., Springate, B., Moscufo, N., Wakefield, D. B., Guttmann, C. R. G., & Wolfson, L. (2014). Processing speed in normal aging: Effects of white matter hyperintensities and hippocampal volume loss. *Aging, Neuropsychology, and Cognition, 21*(2), 197-213. doi:10.1080/13825585.2013.795513

Park, D. C., & Bischof, G. N. (2013). The aging mind: Neuroplasticity in response to cognitive training. *Dialogues in Clinical Neuroscience, 15*(1), 109. doi:10.31887/DCNS.2013.15.1/dpark

Parodi, J. F., Nieto-Gutierrez, W., Tellez, W. A., Ventocilla-Gonzales, I., Runzer-Colmenares, F. M., & Taype-Rondán, Á. (2018). Gait speed and the appearance of neurocognitive disorders in older adults: Results of a Peruvian cohort. *Revista Española de Geriatría y Gerontología, 53*(2), 73-76. doi:10.1016/j.regg.2017.08.001

Pedersen, N. L., & Gerritsen, L. (2015). Genetics of brain and cognitive aging: Introduction to the special issue of Neuropsychology Review. *Neuropsychology Review, 25*(1), 1-2. doi:10.1007/s11065-015-9282-0

Peeters, G., Kenny, R. A., & Lawlor, B. (2020). Late life education and cognitive function in older adults. *International Journal of Geriatric Psychiatry, 35*(6), 633-639. doi:10.1002/gps.5281

Perera, S., Patel, K. V., Rosano, C., Rubin, S. M., Satterfield, S., Harris, T., Ensrud, K., Orwoll, E., Lee, C. G., Chandler, J. M., Newman, A. B., Cauley, J. A., Guralnik, J. M., Ferrucci, L., & Studenski, S. A. (2016). Gait speed predicts incident disability: A pooled analysis. *Journals of Gerontology: Series A, 71*(1), 63-71. doi:10.1093/gerona/glv126

Pérez-Zepeda, M. U., Cesari, M., & García-Peña, C. (2016). Predictive value of frailty indices for adverse outcomes in older adults. *Revista de Investigación Clínica, 68*(2), 92-98.

Pietrzak, R. H., Lim, Y. Y., Ames, D., Harrington, K., Restrepo, C., Martins, R. N., Rembach, A., Laws, S. M., Masters, C. L., Villemagne, V. L., Rowe, C. R., & Maruff, P. (2015). Trajectories of memory decline in preclinical Alzheimer's disease: Results from the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing. *Neurobiology of Aging, 36*(3), 1231-1238. doi:10.1016/j.neurobiolaging.2014.12.015

Pike, C. J. (2017). Sex and the development of Alzheimer's disease. *Journal of Neuroscience Research, 95*(1-2), 671-680. doi:10.1002/jnr.23827

Pilotto, A., Franceschi, M., Leandro, G., Di Mario, F., & Geriatric Gastroenterology Study Group (Società Italiana di Gerontologia e Geriatria) (2003). NSAID and aspirin use by the elderly in general practice: Effect on gastrointestinal symptoms and therapies. *Drugs & Aging, 20*(9), 701–710. doi:10.2165/00002512-200320090-00006

Piumatti, G., Moore, S. C., Berridge, D. M., Sarkar, C., & Gallacher, J. (2018). The relationship between alcohol use and long-term cognitive decline in middle and late life: A longitudinal analysis using UK Biobank. *Journal of Public Health, 40*(2), 304-311. doi:10.1093/pubmed/fdx186

Plomin, R., & Deary, I. J. (2014). Genetics and intelligence differences: Five special findings. *Molecular Psychiatry, 20*, 98. doi:10.1038/mp.2014.105

Podcasy, J. L., & Epperson, C. N. (2016). Considering sex and gender in Alzheimer disease and other dementias. *Dialogues in Clinical Neuroscience, 18(*4), 437-446. doi:10.31887/DCNS.2016.18.4/cepperson

Proulx, C. M., Curl, A. L., & Ermer, A. E. (2018). Longitudinal associations between formal volunteering and cognitive functioning. *The Journals of Gerontology: Series B, 73*(3), 522-531. doi:10.1093/geronb/gbx110

R Development Core Team. (2015). *R: A language and environment for statistical computing.* Vienna, Austria: R Foundation for Statistical Computing.

Ram, N., & Grimm, K. J. (2009). Growth mixture modeling: A method for identifying differences in longitudinal change among unobserved groups. *International Journal of Behavioural Development, 33*(6), 565-576. doi:10.1177/0165025409343765

Rantakokko, M., Mänty, M., & Rantanen, T. (2013). Mobility decline in old age. *Exercise and Sport Sciences Reviews, 41*(1). doi:10.1097/JES.0b013e3182556f1e

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience & Biobehavioral Reviews, 30*(6), 730-748. doi:10.1016/j.neubiorev.2006.07.001

Raz, N., Dahle, C. L., Rodrigue, K. M., Kennedy, K. M., & Land, S. (2011). Effects of age, genes, and pulse pressure on executive functions in healthy adults. *Neurobiology of Aging, 32*(6), 1124-1137. doi:10.1016/j.neurobiologaging.2009.05.015

Reas, E. T., Laughlin, G. A., Kritz-Silverstein, D., Barrett-Connor, E., & McEvoy, L. K. (2016). Moderate, regular alcohol consumption is associated with higher cognitive function in older community-dwelling adults. *The Journal of Prevention of Alzheimer's Disease, 3*(2), 105-113. doi:10.14283/jpad.2016.89

Rehm, J., Baliunas, D., Brochu, S., Fischer, B. et al. (2006). *The Costs of Substance Abuse in Canada, 2002.* Highlights. Ottawa ON: Canadian Centre on Substance Abuse.

Rehm, J., Hasan, O. S. M., Black, S. E., Shield, K. D., & Schwarzinger, M. (2019). Alcohol use and dementia: A systematic scoping review. *Alzheimer's Research & Therapy, 11*(1), 1. doi:10.1186/s13195-018-0453-0

Reitz, C. (2016). Toward precision medicine in Alzheimer's disease. *Annals of Translational Medicine, 4*(6), 107-107. doi:10.21037/atm.2016.03.05

Rice, M. E., & Harris, G. T. (2005). Comparing effect sizes in follow-up studies: ROC Area, Cohen's d, and r. *Law Hum Behav, 29*(5), 615-620. doi:10.1007/s10979-005-6832-7

Richard, E. L., Kritz-Silverstein, D., Laughlin, G. A., Fung, T. T., Barrett-Connor, E., & McEvoy, L. K. (2017). Alcohol intake and cognitively healthy longevity in community-dwelling adults: The Rancho Bernardo Study. *Journal of Alzheimer's Disease, 59,* 803-814. doi:10.3233/JAD-161153

Riedel, B. C., Thompson, P. M., & Brinton, R. D. (2016). Age, APOE and sex: Triad of risk of Alzheimer's disease. *The Journal of Steroid Biochemistry and Molecular Biology, 160,* 134-147. doi:10.1016/j.jsbmb.2016.03.012

Roberts, M. H., & Mapel, D. W. (2012). Limited lung function: Impact of reduced peak expiratory flow on health status, health-care utilization, and expected survival in older adults. *American Journal of Epidemiology, 176*(2), 127-134. doi:10.1093/aje/kwr503

Robertson, D. A., Savva, G. M., & Kenny, R. A. (2013). Frailty and cognitive impairment—A review of the evidence and causal mechanisms. *Ageing Research Reviews, 12*(4), 840-851. doi:10.1016/j.arr.2013.06.004

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: A systematic review and meta-analysis. *Psychological Medicine, 44*(10), 2029. doi:10.1017/S0033291713002535

Rockwood, K., & Mitnitski, A. (2006). Limits to deficit accumulation in elderly people. *Mechanisms of Ageing and Development, 127*(5), 494-496. doi:10.1016/j.mad.2006.01.002

Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. *The Journals of Gerontology: Series A, 62*(7), 722-727. doi:10.1093/gerona/62.7.722

Rockwood, K., & Mitnitski, A. (2011). Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clinics in Geriatric Medicine, 27*(1), 17-26. doi:10.1016/j.cger.2010.08.008

Rockwood, K., Andrew, M., & Mitnitski, A. (2007). A comparison of two approaches to measuring frailty in elderly people. *The Journals of Gerontology: Series A, 62A*. doi:10.1093/gerona/62.7.738

Rockwood, K., Blodgett, J. M., Theou, O., Sun, M. H., Feridooni, H. A., Mitnitski, A., Rose, R. A., Godin, J., Gregson, E., & Howlett, S. E. (2017). A frailty index based on deficit accumulation quantifies mortality risk in humans and in mice. *Scientific Reports, 7*, 43068. doi:10.1038/srep43068

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association Journal, 173*(5), 489-495. doi:10.1503/cmaj.050051

Rogers, N. T., Steptoe, A., & Cadar, D. (2017). Frailty is an independent predictor of incident dementia: Evidence from the English Longitudinal Study of Ageing. *Scientific Reports, 7*(1), 15746. doi:10.1038/s41598-017-16104-y

Rolfson, D. B., Wilcock, G., Mitnitski, A., King, E., de Jager, C. A., Rockwood, K., Fallah, N., & Searle, S. D. (2013). An assessment of neurocognitive speed in relation to frailty. *Age & Ageing, 42*(2), 191-196. doi:10.1093/ageing/afs185

Rosano, C., & Snitz, B. E. (2018). Predicting dementia from decline in gait speed: are we there yet? *Journal of the American Geriatrics Society, 66*(9), 1659. doi:10.1111/jgs.15368

Rosano, C., Studenski, S. A., Aizenstein, H. J., Boudreau, R. M., Longstreth Jr, W. T., & Newman, A. B. (2011). Slower gait, slower information processing and smaller prefrontal area in older adults. *Age & Ageing, 41*(1), 58-64. doi:10.1093/ageing/afr113

Ross, L. A., Sprague, B. N., Phillips, C. B., O'Connor, M. L., & Dodson, J. E. (2016). The impact of three cognitive training interventions on older adults' physical functioning across 5 years. *Journal of Aging and Health, 30*(3), 475-498. doi:10.1177/0898264316682916

Rosso, A. L., Taylor, J. A., Tabb, L. P., & Michael, Y. L. (2013). Mobility, disability, and social engagement in older adults. *Journal of Aging and Health, 25*(4), 617-637. doi:10.1177/0898264313482489

Rothman, M. D., Leo-Summers, L., & Gill, T. M. (2008). Prognostic significance of potential frailty criteria. *Journal of the American Geriatrics Society, 56*(12), 2211-2216. doi:10.1111/j.1532-5415.2008.02008.x

Rothman, S. M., & Mattson, M. P. (2013). Activity-dependent, stress-responsive BDNF signaling and the quest for optimal brain health and resilience throughout the lifespan. *Neuroscience, 239*, 228-240. doi:10.1016/j.neuroscience.2012.10.014

Rugg, M. D., & Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Current Opinion in Neurobiology, 23*(2), 255-260. doi:10.1016/j.conb.2012.11.005

Ryan, L., Hay, M., Huentelman, M. J., Duarte, A., Rundek, T., Levin, B., Soldan, A., Pettigrew, C., Mehl, M. R., & Barnes, C. A. (2019). Precision aging: applying precision medicine to the field of cognitive aging. *Frontiers in Aging Neuroscience, 11*, 128. doi:10.3389/fnagi.2019.00128

Sabia, S., Elbaz, A., Britton, A., Bell, S., Dugravot, A., Shipley, M., Kivimaki, M., & Singh-Manoux, A. (2014). Alcohol consumption and cognitive decline in early old age. *Neurology, 82*(4), 332. doi:10.1212/WNL.0000000000000063

Sachdeva, A., Chandra, M., Choudhary, M., Dayal, P., & Anand, K. S. (2016). Alcohol-related dementia and neurocognitive impairment: A review study. *International Journal of High-Risk Behaviors & Addiction, 5*(3). doi:10.5812/ijhrba.27976

Sadanand, S., Balachandar, R., & Bharath, S. (2016). Memory and executive functions in persons with type 2 diabetes: A meta-analysis. *Diabetes/Metabolism Research and Reviews, 32(*2), 132-142. doi:10.1002/dmrr.2664

Sala, G., & Gobet, F. (2019). Cognitive training does not enhance general cognition. *Trends in Cognitive Sciences, 23*(1), 9-20. doi:10.1016/j.tics.2018.10.004

Salgado, J. F. (2018). Transforming the area under the normal curve (AUC) into Cohen'sd, Pearson's rpb, odds-ratio, and natural log odds-ratio: Two conversion tables. *European Journal of Psychology Applied to Legal Context, 10*(1), 35-47. doi:10.5093/ejpalc2018a5

Salthouse, T. A. (1991). *Theoretical perspectives on cognitive aging*. Hillsdale, N.J.: L. Erlbaum Associates.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review, 103*(3), 403-428. doi:10.1037/0033-295x.103.3.403

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging, 30*(4), 507-514. doi:10.1016/j.neurobiolaging.2008.09.023

Santos-Eggimann, B., Cuénoud, P., Spagnoli, J., & Junod, J. (2009). Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *Journal of Gerontology: Series A, 64*(6), 675-681. doi:10.1093/gerona/glp012

Sapkota, S., Bäckman, L., & Dixon, R. A. (2017). Executive function performance and change in aging is predicted by apolipoprotein E, intensified by catechol-O-methyltransferase, and brain-derived neurotrophic factor, and moderated by age and lifestyle. *Neurobiology of Aging, 52*, 81-89. doi:10.1016/j.neurobiolaging.2016.12.002

Satariano, W. A., Kealey, M., Hubbard, A., Kurtovich, E., Ivey, S. L., Bayles, C. M., Hunter, R. H., & Prohaska, T. R. (2016). Mobility disability in older adults: At the intersection of people and places. *The Gerontologist, 56*(3), 525-534. doi:10.1093/geront/gnu094

Sattler, C., Toro, P., Schönknecht, P., & Schröder, J. (2012). Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. *Psychiatry Research, 196*(1), 90-95. doi:10.1016/j.psychres.2011.11.012

Saxby, B. K., Harrington, F., McKeith, I. G., Wesnes, K., & Ford, G. A. (2003). Effects of hypertension on attention, memory, and executive function in older adults. *Health Psychology, 22*(6), 587. doi:10.1080/03610731003613482

Schneeweis, N., Skirbekk, V., & Winter-Ebmer, R. (2014). Does education improve cognitive performance four decades after school completion? *Demography, 51*(2), 619-643. doi:10.1007/s13524-014-0281-1

Searle, S., Mitnitski, A., Gahbauer, E., Gill, T., & Rockwood, K. (2008). A standard procedure for creating a frailty index. *BMC Geriatrics., 8*(24). doi:10.1186/1471-2318-8-24

Seligman, M. E., & Csikszentmihalyi, M. (2014). *Positive Psychology: An Introduction In Flow and the Foundations of Positive Psychology* (pp. 279-298). Springer, Dordrecht.

Sexton, C. E., & Yaffe, K. (2019). Population-based approaches to dementia prevention. *Journal of Alzheimer's Disease, 70*, S15-S17. doi:10.3233/JAD-190104

Sha, T., Cheng, W., & Yan, Y. (2018). Prospective associations between pulse pressure and cognitive performance in Chinese middle-aged and older population across a 5-year study period. *Alzheimer's Research & Therapy, 10*(1), 29. doi:10.1186/s13195-018-0355-1

Shaaban, C. E., Jia, Y., Chang, C.-C. H., & Ganguli, M. (2019). Independent and joint effects of vascular and cardiometabolic risk factor pairs for risk of all-cause dementia: A prospective population-based study. *International Psychogeriatrics, 31*(10), 1421-1432. doi:10.1017/S1041610219001066

Shah, H., Albanese, E., Duggan, C., Rudan, I., Langa, K. M., Carrillo, M. C., Chan, K. Y., Joanette, Y., Prince, M., Rossor, M., Saxena, S., Snyder, H. M., Sperling, R., Varghese, M., Wang, H., Wortmann, M., & Dua, R. (2016). Research priorities to reduce the global burden of dementia by 2025. *The Lancet Neurology, 15*(12), 1285-1294. doi:10.1016/S1474-4422(16)30235-6

Shankar, A., McMunn, A., Demakakos, P., Hamer, M., & Steptoe, A. (2017). Social isolation and loneliness: Prospective associations with functional status in older adults. *Health Psychology, 36*(2), 179. doi:10.1037/hea0000437

Shaw, E. E., Schultz, A. P., Sperling, R. A., & Hedden, T. (2015). Functional connectivity in multiple cortical networks is associated with performance across cognitive domains in older adults. *Brain Connectivity, 5*(8), 505-516. doi:10.1089/brain.2014.0327

Sheng, C., Huang, Y., & Han, Y. (2018). Dissection of prodromal Alzheimer's disease. *Frontiers in Bioscience (Landmark edition), 23*, 1272-1291. doi:10.2741/4643.

Shi, S., Afilalo, J., Lipsitz, L. A., Popma, J. J., Khabbaz, K. R., Laham, R. J., Guibone, K., Grodstein, F., Lux, E. &Kim, D. H. (2018). Frailty phenotype and deficit accumulation frailty index in predicting recovery after transcatheter and surgical aortic valve

replacement. *The Journals of Gerontology: Series A, 74(*8), 1249-1256. doi:10.1093/gerona/gly196

Shimada, H., Makizako, H., Doi, T., Yoshida, D., Tsutsumimoto, K., Anan, Y., Uemura, K., Lee, S., Park, H., & Suzuki, T. (2014). A large, cross-sectional observational study of serum BDNF, cognitive function, and mild cognitive impairment in the elderly. *Frontiers in Aging Neuroscience, 6*(69). doi:10.3389/fnagi.2014.00069

Singh-Manoux, A., Dugravot, A., Fournier, A., Abell, J., Ebmeier, K., Kivimäki, M., & Sabia, S. (2017). Trajectories of depressive symptoms before diagnosis of dementia: A 28-year follow-up study. *Journal of the American Medical Association Psychiatry, 74*(7), 712-718. doi:10.1001/jamapsychiatry.2017.0660

Singh-Manoux, A., Dugravot, A., Kauffmann, F., Elbaz, A., Ankri, J., Nabi, H., Kivimaki, M., & Sabia, S. (2010). Association of lung function with physical, mental and cognitive function in early old age. *Age, 33*(3), 385-392. doi:10.1007/s11357-010-9189-x

Singh-Manoux, A., Dugravot, A., Shipley, M., Brunner, E. J., Elbaz, A., Sabia, S., & Kivimaki, M. (2018). Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. *Alzheimer's and Dementia, 14*(2), 178-186. doi:10.1016/j.jalz.2017.06.2637

Small, B. J., Dixon, R. A., & McArdle, J. J. (2011). Tracking cognition–health changes from 55 to 95 years of age. *The Journals of Gerontology: Series B, 66B*(suppl_1), i153-i161. doi:10.1093/geronb/gbq093

Small, B. J., Rosnick, C. B., Fratiglioni, L., & Backman, L. (2004). Apolipoprotein E and cognitive performance: A meta-analysis. *Psychology of Aging, 19*(4), 592-600. doi:10.1037/0882-7974.19.4.592

Smith-Ray, R. L., Hughes, S. L., Prohaska, T. R., Little, D. M., Jurivich, D. A., & Hedeker, D. (2013). Impact of cognitive training on balance and gait in older adults. *Journals of Gerontology: Series B, 70*(3), 357-366. doi:10.1093/geronb/gbt097

Song, X., Mitnitski, A., & Rockwood, K. (2011). Nontraditional risk factors combine to predict Alzheimer disease and dementia. *Neurology, 77.* doi:10.1212/WNL.0b013e318225c6bc

Soysal, P., Veronese, N., Thompson, T., Kahl, K. G., Fernandes, B. S., Prina, A. M., Solmi, M., Schofield, P., Koyanagi, A., Tsend, P-Y., Chu, C-S., Cosco, T. D., Cesari, M., Carvalho, A. F., & Stubbs, B. (2017). Relationship between depression and frailty in older adults: A systematic review and meta-analysis. *Ageing Research Reviews, 36*, 78-87. doi:10.1016/j.arr.2017.03.005

Staal, M. A., Bolton, A. E., Yaroush, R. A., & Bourne Jr, L. E. (2008). Cognitive performance and resilience to stress. In B. J. Luckey & V. Tepe (Eds.), *Biobehavioural Resilience to Stress* (pp. 259-348). Boca Raton: Taylor & Francis Group, LLC.

Statistics Canada. (2016). *Prevalence and Monetary Costs of Dementia in Canada: Population Health Expert Panel.* https://alzheimer.ca/sites/default/files/files/national/statistics/prevalenceandcostsofdementia_en.pdf

Statistics Canada. (2015). *Canada`s Population Estimates: Age and Sex, July 1, 2015.* https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501

Statistics Canada. (2016). *Disability in Canada: Initial findings from the Canadian Survey on Disability.* https://www150.statcan.gc.ca/n1/pub/89-654-x/89-654-x2013002-eng.htm

Statistics Canada. (2017). *Canadian Tobacco Alcohol and Drugs (CTADS): 2015 summary.* https://www.canada.ca/en/health-canada/services/canadian-tobacco-alcohol-drugs-survey/2015-summary.html

Staudinger, U. M., & Greve, W. (2015). Resilience and aging. In N. A. Pachana (Ed.), *Encyclopedia of Geropsychology* (pp. 1-9). Springer Science + Business Media. doi:10.1007/978-981-287-080-3_122-1

Stekhoven, D. J., & Bühlmann, P. (2012). MissForest—non-parametric missing value imputation for mixed-type data. *Bioinformatics, 28*(1), 112-118. doi:10.1093/bioinformatics/btr597

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology, 11*(11), 1006-1012. doi:10.1016/S1474-4422(12)70191-6

Sternäng, O., Reynolds, C. A., Finkel, D., Ernsth-Bravell, M., Pedersen, N. L., & Dahl Aslan, A. K. (2015). Grip strength and cognitive abilities: Associations in old age. *The Journals of Gerontology: Series B, 71*(5). doi:10.1093/geronb/gbv017

Storsve, A. B., Grydeland, H., Sneve, M. H., Walhovd, K. B., & Fjell, A. M. (2016). The disconnected brain and executive function decline in aging. *Cerebral Cortex, 27*(3), 2303-2317. doi:10.1093/cercor/bhw082

Stow, D., Matthews, F. E., Barclay, S., Iliffe, S., Clegg, A., De Biase, S., Robinson, L., & Hanratty, B. (2018). Evaluating frailty scores to predict mortality in older adults using data from population based electronic health records: case control study. *Age and Ageing, 47*(4), 564–569. doi:10.1093/ageing/afy022

Stow, D., Matthews, F. E., & Hanratty, B. (2018). Frailty trajectories to identify end of life: A longitudinal population-based study. *BMC Medicine, 16*(1), 171. doi:10.1186/s12916-018-1148-x

Strobl, C., Boulesteix, A.-L., Zeileis, A., & Hothorn, T. (2007). Bias in random forest variable importance measures: Illustrations, sources and a solution. *BMC Bioinformatics, 8*(1), 1-21. doi:10.1186/1471-2105-8-25

Strobl, C., Hothron, T., & Zeileis, A. (2009). Party on! A new, conditional variable-importance measure for random forests available in the party package. *R Journal, 1*, 14-17. doi:10.32614/RJ-2009-013

Strobl, C., Malley, J., & Tutz, G. (2009). An introduction to recursive partitioning: Rationale, application and characteristics of classification and regression trees, bagging and random forests. *Psychological Methods, 14*(4), 323-348. doi:10.1037/a0016973

Studenski, S., Perera, S., Patel, K., Rosano, C., Faulkner, K., Inzitari, M., Brach, J., Chandler, J., Cawthorn, P., Connor, E. B., Nevitt, M, Visser, M., Kritchevsky, S., Badinelli, S., Harris, T., Newman, A. B., Cauley, J., Ferrucci, L., & Guralnik, J. (2011). Gait speed and survival in older adults. *Journal of the American Medical Association, 305*(1), 50-58. doi:10.1001/jama.2010.1923

Subramaniapillai, S., Rajagopal, S., Elshiekh, A., Pasvanis, S., Ankudowich, E., & Rajah, M. N. (2019). Sex differences in the neural correlates of age-related episodic memory decline. *Journal of Cognitive Neuroscience, 31*(12), 1895-1916. doi:10.1162/jocn_a_01455

Swanberg, M. M., Tractenberg, R. E., Mohs, R., Thal, L. J., & Cummings, J. L. (2004). Executive dysfunction in Alzheimer disease. *Archives of Neurology, 61*(4), 556-560. doi:10.1001/archneur.61.4.556

Swank, C., Almutairi, S., & Medley, A. (2017). Proposing development and utility of a mobility composite measure in patients with a neurologic disorder. *Rehabilitation Research and Practice, 2017*. doi:10.1155/2017/8619147

Szekely C.A, Breitner J.C.S., Fitzpatrick A.L., (2008). NSAID use and dementia risk in the Cardiovascular Health Study: Role of APOE and NSAID type. *Neurology, 7,* 17–24. doi:10.1212/01.wnl.0000284596.95156.48

Taylor, S. F., Kornblum, S., Lauber, E. J., Minoshima, S., & Koeppe, R. A. (1997). Isolation of specific interference processing in the Stroop task: PET activation studies. *Neuroimage, 6*(2), 81-92. doi:10.1006/nimg.1997.0285

Theou, O., Cann, L., Blodgett, J., Wallace, L. M. K., Brothers, T. D., & Rockwood, K. (2015). Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the Survey of Health, Ageing, and Retirement in Europe. *Ageing Research Reviews, 21*, 78-94. doi:10.1016/j.arr.2015.04.001

Thibeau, S., McDermott, K., McFall, G. P., Rockwood, K., & Dixon, R. A. (2019). Frailty effects on non-demented cognitive trajectories are moderated by sex and Alzheimer's genetic risk. *Alzheimer's Research & Therapy, 11*(1), 55. doi:10.1186/s13195-019-0509-9

Thibeau, S., McFall., G. P., Camicioli, R., Dixon, R. A. (2019). Physical activity and mobility differentially predict nondemented executive function trajectories: Do sex and *APOE* moderate these associations? *Gerontology, 65*, 640-648. doi:10.1159/000496442

Thibeau, S., McFall, G. P., Wiebe, S. A., Anstey, K. J., & Dixon, R. A. (2016). Genetic factors moderate everyday physical activity effects on executive function in aging: Evidence from the Victoria Longitudinal Study. *Neuropsychology, 30*(1), 6-17. doi:10.1037/neu0000217

Thibeau, S., McFall, G. P., Wiebe, S. A., Camicioli, R., & Dixon, R. A. (2017). Alzheimer's disease biomarkers interactively influence physical activity, mobility, and cognition associations in a non-demented population. *Journal of Alzheimer's Disease, 60*(1), 69-86. doi:10.3233/JAD-170130

Thow, M. E., Summers, M. J., Saunders, N. L., Summers, J. J., Ritchie, K., & Vickers, J. C. (2018). Further education improves cognitive reserve and triggers improvement in selective cognitive functions in older adults: The Tasmanian Healthy Brain Project. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 10*, 22-30. doi:10.1016/j.dadm.2017.08.004

Tian, Q., Chastan, N., Bair, W.-N., Resnick, S. M., Ferrucci, L., & Studenski, S. A. (2017). The brain map of gait variability in aging, cognitive impairment and dementia—A systematic review. *Neuroscience & Biobehavioral Reviews, 74,* 149-162. doi:10.1016/j.neubiorev.2017.01.020

Tierney, M. C., Curtis, A. F., Chertkow, H., & Rylett, R. J. (2017). Integrating sex and gender into neurodegeneration research: A six-component strategy. *Alzheimer's & Dementia: Translational Research & Clinical Interventions, 3*(4), 660-667. doi:10.1016/j.trci.2017.10.006

Toh, Y. L., Ng, T., Tan, M., Tan, A., & Chan, A. (2018). Impact of brain-derived neurotrophic factor genetic polymorphism on cognition: A systematic review. *Brain and Behavior, 8*(7), e01009-e01009. doi:10.1002/brb3.1009

Tomioka, K., Kurumatani, N., & Hosoi, H. (2016). Social participation and cognitive decline among community-dwelling older adults: A community-based longitudinal study. *The Journals of Gerontology: Series B, 73*(5), 799-806. doi:10.1093/geronb/gbw059

Toohey, A. M., McCormack, G. R., Doyle-Baker, P. K., Adams, C. L., & Rock, M. J. (2013). Dog-walking and sense of community in neighborhoods: Implications for promoting regular physical activity in adults 50 years and older. *Health & Place, 22*, 75-81. doi:10.1016/j.healthplace.2013.03.007

Topiwala, A., & Ebmeier, K. P. (2018). Effects of drinking on late-life brain and cognition. *Evidence Based Mental Health, 21*(1), 12. doi:10.1136/eb-2017-102820

Topiwala, A., Allan, C. L., Valkanova, V., Zsoldos, E., Filippini, N., Sexton, C., Fooks, P., Singh-Manoux, A., Mackay, C. E., Kivimäki, M., & Ebmeier, K. P. (2017). Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: Longitudinal cohort study. *BMJ, 357*, j2353. doi:10.1136/bmj.j2353

Trevisan, C., Rizzuto, D., Sergi, G., Maggi, S., Welmer, A.-K., & Vetrano, D. L. (2020). Peak expiratory flow, walking speed and survival in older adults: An 18-year longitudinal population-based study. *Experimental Gerontology, 135*, 110941. doi:10.1016/j.exger.2020.110941

Tromp, D., Dufour, A., Lithfous, S., Pebayle, T., & Després, O. (2015). Episodic memory in normal aging and Alzheimer disease: Insights from imaging and behavioral studies. *Ageing Research Reviews, 24*, 232-262. doi:10.1016/j.arr.2015.08.006

United Nations, Department of Economic and Social Affairs, Population Division. (2019). *World population prospects 2019: Highlights* (ST/ESA/SER.A/423). New York, NY. https://population.un.org/wpp/Publications/Files/WPP2019_Highlights.pdf

United Nations. (2015). *World Population Ageing 2015*. https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf

Van Boxtel, M. P. J., Langerak, K., Houx, P. J., & Jolles, J. (1996). Self-reported physical activity, subjective health, and cognitive performance in older adults. *Experimental Aging Research, 22*(4), 363-379. doi:10.1080/03610739608254017

van Gelder, B. M., Tijhuis, M., Kalmijn, S., Giampaoli, S., Nissinen, A., & Kromhout, D. (2006). Marital status and living situation during a 5-year period are associated with a subsequent 10-year cognitive decline in older men: The FINE Study. *The Journals of Gerontology: Series B, 61*(4), P213-P219. doi:10.1093/geronb/61.4.P213

Varma, V. R., Hausdorff, J. M., Studenski, S. A., Rosano, C., Camicioli, R., Alexander, N. B., Chen, W. G., Lipsitz, L. A., & Carlson, M. C. (2016). Aging, the central nervous system, and mobility in older adults: Interventions. *Journals of Gerontology: Series A, 71*(11), 1451-1458. doi:10.1093/gerona/glw080

Verghese, J., Mahoney, J., Ambrose, A. F., Wang, C., & Holtzer, R. (2010). Effect of cognitive remediation on gait in sedentary seniors. *Journals of Gerontology: Series A, 65(*12), 1338-1343. doi:10.1093/gerona/glq127

Verghese, J., Robbins, M., Holtzer, R., Zimmerman, M., Wang, C., Xue, X., & Lipton, R. B. (2008). Gait dysfunction in mild cognitive impairment syndromes. *Journal of the American Geriatrics Society, 56*(7), 1244-1251. doi:10.1111/j.1532-5415.2008.01758.x

Verghese, J., Wang, C., Lipton, R. B., Holtzer, R., & Xue, X. (2007). Quantitative gait dysfunction and risk of cognitive decline and dementia. *Journal of Neurology, Neurosurgery, and Psychiatry, 78*(9), 929-935. doi:10.1136/jnnp.2006.106914

Verhaeghen, P. (2013). The Elements of Cognitive Aging: Meta-Analyses of Age-Related Differences in Processing Speed and Their Consequences, Oxford University Press. doi:10.1093/acprof:oso/9780195368697.001.0001

Wagner, M., Helmer, C., Tzourio, C., Berr, C., Proust-Lima, C., & Samieri, C. (2018). Evaluation of the concurrent trajectories of cardiometabolic risk factors in the 14 years

before dementia. *Journal of the American Medical Association Psychiatry, 75*(10), 1033-1042. doi:10.1001/jamapsychiatry.2018.2004 %J JAMA Psychiatry

Wagnild, G. M., & Collins, J. A. (2009). Assessing resilience. *Journal of Psychosocial Nursing and Mental Health Services, 47(*12), 28-33. doi:10.3928/02793695-20091103-01

Waljee, A. K., Mukherjee, A., Singal, A. G., Zhang, Y., Warren, J., Balis, U., Marrero, J., & Higgins, P. D. (2013). Comparison of imputation methods for missing laboratory data in medicine. *BMJ Open, 3*(8), e002847. doi:10.1136/bmjopen-2013-002847

Wallace, L. M. K., Theou, O., Godin, J., Andrew, M. K., Bennett, D. A., & Rockwood, K. (2019). Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. *The Lancet Neurology, 18*(2), 177-184. doi:10.1016/S1474-4422(18)30371-5

Wang, W., & Cabeza, R. (2016). Episodic memory and its neural mechanisms. In R. Cabeza, L. Nyberg, & D. Park (Eds.) *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*. New York, NY. Oxford University Press.

Warren, M., Ganley, K. J., & Pohl, P. S. (2016). The association between social participation and lower extremity muscle strength, balance, and gait speed in US adults. *Preventive Medicine Reports, 4*, 142-147. doi:10.1016/j.pmedr.2016.06.005

Watt, R. G., Heilmann, A., Sabbah, W., Newton, T., Chandola, T., Aida, J., Sheiham, A., Marmot, M., Kawachi, I., & Tsakos, G. (2014). Social relationships and health related behaviors among older US adults. *BMC Public Health, 14*(1), 533. doi:10.1186/1471-2458-14-533

Wearing, J., Konings, P., Stokes, M., & de Bruin, E. D. (2018). Handgrip strength in old and oldest old Swiss adults–a cross-sectional study. *BMC Geriatrics, 18*(1), 266. doi:10.1093/geronb/gbz072

Webber, S. C., Porter, M. M., & Menec, V. H. (2010). Mobility in older adults: A comprehensive framework. *Gerontologist, 50*(4), 443-450. doi:10.1093/geront/gnq013

Weber, D. (2016). Social engagement to prevent cognitive ageing? *Age and Ageing, 45*(4), 441-442. doi:10.1093/ageing/afw083

Wei, J., Ying, M., Xie, L., Chandrasekar, E. K., Lu, H., Wang, T., & Li, C. (2019). Late-life depression and cognitive function among older adults in the U.S.: The National Health and Nutrition Examination Survey, 2011–2014. *Journal of Psychiatric Research, 111,* 30-35. doi:10.1016/j.jpsychires.2019.01.012

Weinstein, G., Beiser, A. S., Choi, S. H., Preis, S. R., Chen, T. C., Vorgas, D., Ay, R., Pikula, A., Wolf, P. A., DeStefano, A. L., Vasan, R. S., & Seshadri, S. (2014). Serum brain-derived neurotrophic factor and the risk for dementia: The Framingham Heart Study. *JAMA Neurology, 71*(1), 55-61. doi:10.1001/jamaneurol.2013.4781

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin Journal, 120*(2), 272-292. doi:10.1037/0033-2909.120.2.272

White, D. K., Neogi, T., Nevitt, M. C., Peloquin, C. E., Zhu, Y., Boudreau, R. M., Cauley, J., Ferrucci, L., Harris, T. B., Satterfield, S. M., Simonsick, E. M., Strotmeyer, E. S., & Zhang, Y. (2013). Trajectories of gait speed predict mortality in well-functioning older adults: The Health, Aging and Body Composition study. *The Journals of Gerontology: Series A, 68*(4), 456–464. doi:10.1093/gerona/gls197

Whitson, H. E., Duan-Porter, W., Schmader, K. E., Morey, M. C., Cohen, H. J., & Colón-Emeric, C. S. (2016). Physical resilience in older adults: Systematic review and development of an emerging construct. *The Journals of Gerontology: Series A, 71(*4), 489-495. doi:10.1093/gerona/glv202

Widagdo, I. S., Pratt, N., Russell, M., & Roughead, E. E. (2016). Construct validity of four frailty measures in an older Australian population: A Rasch analysis. *The Journal of Frailty & Aging,* 5(2), 78-81. doi:10.14283/jfa.2016.83

Willey, J. Z., Gardener, H., Caunca, M. R., Moon, Y. P., Dong, C., Cheung, Y. K., Sacco, R. L., Elkind, M. S. V., & Wright, C. B. (2016). Leisure-time physical activity associates with cognitive decline. *The Northern Manhattan Study, 86*(20), 1897-1903. doi:10.1212/wnl.0000000000002582

Willis, S. L., Schaie, K. W., & Martin, M. (2009). Cognitive plasticity. In V. Bengston, M. Silverstein, N. Putney, & D. Gans (Eds.), *Handbook of Theories of Aging* (pp. 295-322). New York: Springer Publishing.

Wilson, R. S., Leurgans, S. E., Boyle, P. A., & Bennett, D. A. (2011). Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. *Archives of Neurology, 68*(3), 351-356. doi:10.1001/archneurol.2011.31

Wilson, R. S., Yu, L., Lamar, M., Schneider, J. A., Boyle, P. A., & Bennett, D. A. (2019). Education and cognitive reserve in old age. *Neurology, 92*(10), e1041-e1050.

Wisdom, N. M., Callahan, J. L., & Hawkins, K. A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiology of Aging, 32*(1), 63-74. doi:10.1016/j.neurobiolaging.2009.02.003

Wongrakpanich, S., Wongrakpanich, A., Melhado, K., & Rangaswami, J. (2018). A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. *Aging and Disease, 9*(1), 143–150. doi:10.14336/AD.2017.0306

World Health Organization. (2015). *World Report on Ageing and Health.* http://apps.who.int/iris/bitstream/10665/186463/1/9789240694811_eng.pdf?ua=1

World Health Organization. (2018). *Top 10 causes of death.* http://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/

World Health Organization. (2019). *Risk reduction of cognitive decline and dementia: WHO guidelines*. https://apps.who.int/iris/bitstream/handle/10665/312180/9789241550543-eng.pdf?ua=1

Wu, M.-S., Lan, T.-H., Chen, C.-M., Chiu, H.-C., & Lan, T.-Y. (2011). Socio-demographic and health-related factors associated with cognitive impairment in the elderly in Taiwan. *BMC Public Health, 11*(1), 22. doi:10.1186/1471-2458-11-22

Xu, W., Tan, L., Wang, H.-F., Jiang, T., Tan, M.-S., Tan, L., Zhao, Q.-F., Li, J.-Q., Wang, J., & Yu, J.-T. (2015). Meta-analysis of modifiable risk factors for Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 86*(12), 1299-1306. doi:10.1136/jnnp-2015-310548

Yates, L. A., & Orrell, M. (2016). Cognitive leisure activities and future risk of cognitive impairment and dementia: Systematic review and meta-analysis. *International Psychogeriatrics, 28*(11), 1791-1806. doi:10.1017/S1041610216001137

Yeung, S. E., Fischer, A. L., & Dixon, R. A. (2009). Exploring effects of type 2 diabetes on cognitive functioning in older adults. *Neuropsychology, 23*(1), 1-9. doi:10.1037/a0013849

Yuan, P., & Raz, N. (2014). Prefrontal cortex and executive functions in healthy adults: a meta-analysis of structural neuroimaging studies. *Neuroscience & Biobehavioral Reviews, 42*, 180-192. doi:10.1016/j.neubiorev.2014.02.005

Zahodne, L. B., & Zajacova, A. (2020). Education and cognitive aging: An introduction to the special section. *The Journals of Gerontology: Series B, 75*(7), e78-e80. doi:10.1093/geronb/gbaa091

Zammit, A. R., Robitaille, A., Piccinin, A. M., Muniz-Terrera, G., & Hofer, S. M. (2018). Associations between aging-related changes in grip strength and cognitive function in older adults: A systematic review. *The Journals of Gerontology: Series A, 74*(4), 519-527. doi:10.1093/gerona/gly046

Zandi, P.P., Anthony, J.C., Hayden, K.M. (2002). Reduced incidence of AD with NSAID but not H2 receptor antagonists: The Cache county study. *Neurology, 59*,880–6. 27. doi:10.1212/wnl.59.6.880

Zaninotto, P., Batty, G. D., Allerhand, M., & Deary, I. J. (2018). Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. *Journal of Epidemiology and Community Health, 72*(8), 685. doi:10.1136/jech-2017-210116

Zhao, E., Tranovich, M. J., & Wright, V. J. (2014). The role of mobility as a protective factor of cognitive functioning in aging adults: A review. *Sports Health, 6*(1), 63-69. doi:10.1177/1941738113477832