CHARACTERIZING THE LIFESTYLE ENGAGEMENT OF OLDER ADULTS: IMPLICATIONS FOR COGNITIVE FUNCTIONING, PHYSICAL FRAILTY, AND FUTURE INTERVENTIONS

by
Kyle David Moored

A dissertation submitted to The Johns Hopkins University in conformity with the requirements

for the degree of Doctor of Philosophy

Baltimore, Maryland
July 2020

Abstract

Background: Active life-expectancies post-retirement have increased, allowing for new opportunities for cognitive, social, and physical engagement to mitigate later-life health outcomes. The question remains as to how we use information about older adults' lifestyle engagement to predict health outcomes and deploy interventions. Here we characterized qualitatively-distinct lifestyle engagement groups of older adults, and examined whether they had differential risk for cognitive and physical outcomes.

Method: Data come from the Ginkgo Evaluation of Memory Study (N=3,069). Data collection occurred from September 2000 and April 2008. Participants were assessed up to 7.5 years. Baseline activities were measured using the Lifestyle Activity Questionnaire. We conducted latent class analysis to group individuals by their activity response patterns, and examined their risk of dementia using discrete-time proportional hazards modeling. Dementia was screened for every six months and clinically-adjudicated. We then examined whether the lifestyle engagement groups also had differential changes in domain-specific cognition and physical frailty criteria using mixed effects modeling. All models were adjusted for baseline age, sex, race, education, study site, treatment group, medical comorbidities, and depressive symptoms.

Results: A 4-class model adequately characterized lifestyle engagement in the current sample. The Social Intellectual (22%) and Intellectual (18%) groups had high engagement in intellectual activities, whereas the Social Intellectual and Social groups (32%) had high engagement in social institutional activities. The Least Active group (28%) had lower engagement in most activities and had the highest risk of incident dementia. We found that the Social Intellectual group had

higher baseline performance across cognitive domains, as well as attenuated declines in memory. Finally, we found that the Social Intellectual group had lower risk of prevalent slow gait compared to all groups, and lower risk of prevalent exhaustion compared to the Least Active group.

Implications: Older adults who were highly active in intellectual and social institutional activities had the lowest risk of poor health outcomes. Behavioral interventions should aim to supplement an individual's current lifestyle to encourage broad engagement in cognitively- and socially-enriching activities. Future group-level interventions can specifically target the activity types that are meaningful to older adults to facilitate adherence and enjoyment of health-promoting behaviors.

Thesis Advisory Committee
Dr. Michelle Carlson (Advisor), Dr. Karen Bandeen-Roche (Chair), Dr. George Rebok, Dr. Sevil Yasar

Alternates: Dr. Jeanine Parisi, Dr. Roland Thorpe

Acknowledgements

These past four years have been incredibly enriching for my growth as a researcher and individual. I am indebted to so many individuals who have taken the time to make my experiences at Johns Hopkins so much better.

I thank my advisor, Dr. Michelle Carlson. Your support and guidance throughout the years has not only increased my knowledge and skills, but also made me more confident, both in my research and as a leader. I am truly lucky to have you as a mentor.

I thank all members of my committee: Dr. Karen Bandeen-Roche, Dr. Janice Bowie, Dr. Alden Gross, Dr. Jeanine Parisi, Dr. George Rebok, and Dr. Sevil Yasar. All of you have offered crucial advice on my dissertation work, as well as invaluable personal and professional mentorship throughout my years in the program. I will greatly miss catching up with you all in the hallways of the Wolfe St. building, COAH, and Hampton House.

I thank the directors and fellows of the Epidemiology, Biostatistics, and Mental Health of Aging training grant for their academic and financial support throughout my studies. Your rigorous but collegial spirit has only made my work better, and I feel I became even more of a trans-disciplinary researcher thanks to the diverse perspectives brought together by this program.

> I especially thank Andrew Leroux, who collaborated with me on our 360-degree project with the Baltimore Experience Corps accelerometry data.

I also thank the Department of Mental Health for their academic and financial support. My four years in hallways of the 8th floor of Hampton House were always met with enriching conversations and kind faces.

> I thank Patty Scott, Michelle Maffett, Carlina Carter, Candice Davis, and Scott Hubbard for their invaluable administrative support, as well as Dr. Judy Bass for her doctoral guidance.
>
> I thank Dr. Dani Fallin, Dr. Heather Volk, and Dr. Bill Eaton for letting me TA their classes, providing me with a chance to develop my own teaching and mentoring skills.
>
> I also thank Vivian Kardmai, who was always a friendly-face and went above and beyond in ensuring Hampton House a great place to work.

I thank the family of Dr. Paul V. Lemkau, who generously provided a scholarship to support my studies in the Department of Mental Health. It was truly an honor to meet you all and learn more about the ground-breaking work Dr. Lemkau did to establish our department.

I thank the current and former members of the Carlson Lab: Dr. Atif Adam, Dr. Ryan Andrews, Dr. Thomas Chan, Dr. Yi-fang Chuang, Breanna Crane, Brittany Drazich, Dr. Dana Eldreth, Dr. Vijay Varma, and others. Your guidance throughout the years and partnership on various projects was a highlight of my time at Johns Hopkins. I will miss our fun, lively conversations in Hampton House and at lab meetings.

I thank my other research mentors from around the school. Dr. Qian-Li Xue and Dr. Johannes Thrul both provided opportunities to expand my research in novel directions and offered very helpful guidance in learning new methods.

I especially thank the PhD students who provided irreplaceable friendship:

> My PhD cohort (a.k.a., “Cohort of Magnificent People”): Sherri-Chanelle Brighthaupt, Shoshanna Fine, Geoff Kahn, Angela Lin, John Thorne, Kayla Tormohlen, and Dr. Lindsey Webb.
>
> My friends throughout the school: Giselle Casillas, Dr. Alden Lai, Dr. John Levin, Kira Riehm, Emily Smail, Dan Woznica, and many others.
>
> Dr. Nicole Armstrong for her contributions to this dissertation research and lasting friendship.
>
> I feel truly grateful to have gone through this program with you all. I will never forget the fun times we shared throughout these four years and the connection we have.

Thank you to my friends in Baltimore and beyond for your endless support and comradery.

Thank you to the participants of the Ginkgo Evaluation of Memory study, for whom without any of this work would have been possible. I thank you for giving your time and energy for the betterment of science. I also thank the site PIs of this study for their support throughout this process: Dr. Beth Snitz, Dr. Annette Fitzpatrick, Dr. Jeff Williamson, and Dr. Steven DeKosky.

Finally, I am incredibly grateful for my loved-ones. Dave, for your endless companionship through what at-times was a very challenging process. My parents for their unwavering support and love throughout my life, culminating in me writing this dissertation. My sister, Shelby, for lending an ear when I needed it, and for her passion for healthcare that further motivates my own passions. My grandpa, who is one of the most resilient and caring people I know. I would not be where I am today without any of you.

I dedicate this work to you all.

Table of Contents

List of Tables

List of Tables

Chapter 1: Introduction and Specific Aims

1.1. The Problem

The United States is facing an impending aging crisis. The aging "Baby-Boomer" population outnumbers younger demographic groups, resulting in increased prevalence of neurocognitive and mobility impairments (Bartels & Naslund, 2013). There were an estimated 6.08 million individuals in 2017 who had either clinical Alzheimer's Disease (AD), the most common type of dementia, or preclinical mild cognitive impairment (MCI) of AD type in the US alone (Brookmeyer et al., 2018). This number is expected to more than double by 2060 (Brookmeyer et al., 2018). AD is characterized by episodic memory impairments and associated with increased risk for functional impairment, mortality, and reduced quality of life (Alzheimer's Association, 2019). Furthermore, 40% of individuals over 65 have trouble carrying out daily activities (Fried, Bandeen-Roche, Chaves, & Johnson, 2000), and over a third of adults over 70 have a gait abnormality that limits mobility (Verghese et al., 2006). Thus, promoting cognitive and physical health in later life is an important public health effort that would not only encourage functioning and well-being of older adults, but also mitigate the healthcare burden of an aging population.

In the absence of effective pharmaceutical treatments for both aging-related cognitive and mobility impairments (Alzheimer's Association, 2019; Varma, Hausdorff, et al., 2016), clinicians currently encourage prevention through engagement in physical exercise, cognitive training, and control of vascular risk factors (National Academies of Sciences, Engineering, and Medicine, 2017). However, interventions on these factors may sometimes lack of feasibility or acceptability within older populations most at risk (National Academies of Sciences, Engineering, and Medicine, 2017). For example, given only 20% of older adult meet physical

activity guidelines (Varma, Tan, et al., 2016), it may be difficult to encourage sedentary older adults to engage in and sustain novel exercise routines that could further benefit cognitive health (Voss et al., 2011, 2014). Thus, there has been substantial interest in how to leverage enriching lifestyle activities, everyday activities that older individuals commonly engage in, to improve or maintain cognitive health with age (Bennett et al., 2014; Bielak, 2010; Gow et al., 2017; Hertzog et al., 2009; Hultsch et al., 1999a; Salthouse, 2006; Schreiber et al., 2016).

1.2. The Potential of Lifestyle Activities

"Lifestyle activities" are typically considered those that include varying levels of physical, cognitive, and social engagement (Bielak, 2010). For example, playing tennis is a lifestyle activity that requires all three components: 1) physical exercise to traverse the court, 2) selective attention and cognitive-motor integration to locate and hit the ball, and 3) social interaction with your opponent or teammate. In contrast, playing cards is a lifestyle activity that involves physical and cognitive engagement, but very little physical activity.

The use-it-or-lose it (Hultsch et al., 1999a; Salthouse, 2006) and enrichment (Hertzog et al., 2009) hypotheses suggest lifestyle activity engagement, even in later life, is neuroprotective. There are many potential behavioral and neural mechanisms for this relationship (Figure 1.1). Physical (e.g., vascular), cognitive (e.g., behavioral plasticity), social (e.g., social ties and roles), and brain structural and functional changes all may link lifestyle activity engagement to cognitive and motor outcomes. These relationships are further elaborated later in this dissertation. Supporting the use-it-or-lose-it and enrichment hypotheses, inventories measuring engagement in a variety of physically, cognitively, and socially enriching activities have been found to predict neurocognitive outcomes in later life (Bennett et al., 2014; Carlson et al., 2012; Chan et al., 2018; Gow et al., 2017; Moored et al., 2018; Sajeev et al., 2016; Voss et al., 2014).

1.3. Current Dissertation

In this dissertation, we capitalize on a physically and cognitively well-characterized sample of community-dwelling older adults to complement existing research examining individual activities for neurocognitive benefit by asking the following question: **do lifestyle engagement groups of older adults, who differ in amount and types of lifestyle activities, have different physical and cognitive trajectories, as well as different risks of incident dementia over time?**

1.4. Relevance

Increasing active life expectancies post-retirement (Crimmins et al., 2016) offer novel chances for lifestyle activity engagement in older adulthood. Yet, later life is also a period of substantial variability in cognitive and physical functioning (Bandeen-Roche et al., 2015; Fried et al., 1994; Verhaeghen & Salthouse, 1997). Better characterizing and understanding the relationship between lifestyle activity and cognitive and physical functioning outcomes in later life can help inform achievable and more sustainable interventions to promote and maintain health in older adults.

Given that individuals may differ in both the *quantity* (e.g., amount) and *quality* (e.g., types/characteristics) of their engagement, one way of incorporating both differences to potentially better characterize this heterogeneity in lifestyle engagement may be to examine latent groups of individuals who endorse distinct activity response *patterns*. These latent groups are described throughout this dissertation as "lifestyle engagement groups." Highly engaged

lifestyles are thought to place higher demands on physical and cognitive functioning (Carlson & Varma, 2015; Hultsch et al., 1999a; Schooler, 1984; Stern, 2002).

1.4.1. Prior methods used to measure lifestyle engagement. Existing aggregate measures (e.g., *frequency* or *variety* of activity engagement) derived from activity inventories focus on total *amount* of an individual's engagement, but do not consider differences in the specific activities that make up this individual's total engagement. For example, for two individuals with the same activity count (i.e., activity *variety*), one may have reported primarily "sedentary" activities (e.g., watching TV, listening to radio) while the other may have reported more "active" activities (e.g., volunteering, church attendance). While both reported the same number of activities, it could be assumed that the second individual's activities are more protective against health declines (Fried et al., 2004; Reese, Thorpe, Bell, Bowie, & LaVeist, 2012), but this information is lost when a simple count measure is used.

To better account for differences in activity type (e.g., physical, social, sedentary), several prior studies have first grouped activities by type, either using expert consensus (e.g., Aartsen et al., 2002); ratings of cognitive intensity (e.g., Carlson et al., 2012), factor analytic methods (e.g., Lennartsson & Silverstein, 2001), or occasionally simply by a priori . Aggregate *frequency* and *variety* measures can then be derived from these groupings and used to examine whether specific activity types have different relationships with cognition. These aggregate measures and studies incorporating them are reviewed later in this dissertation (see "Measures of lifestyle activity engagement").

1.4.2. Current approach. The approach taken in the current dissertation extends upon these aggregate measures by grouping individuals by their commonly reported activities. We can then examine whether these groups report overlapping and non-overlapping activity types (e.g.,

intellectual, social, physical), and potentially have different trajectories of cognitive and physical health outcomes. Examining lifestyle activity engagement in this way may better capture *qualitative* (e.g., characteristics, types) differences in lifestyle at the group-level that are missed in aggregate activity measures, and which may be relevant for targeting interventions to specific groups of older adults.

To further illustrate how this approach is useful, Figure 1.2 includes a hypothetical example where there are three frequently reported sets of lifestyle activities. Individuals in Group 1 ("home activities only") commonly report engaging in two activities, sewing and reading a book. Groups 2 and 3 both commonly report engaging in four activities, two of which overlap with those commonly reported in Group 1. There is therefore a *quantitative* difference in activity engagement between Group 1 and Groups 2 and 3. However, there are also *qualitative* differences between Group 2 and Group 3 in the remaining two activities that they commonly reported. Individuals in Group 2 ("home + cognitively enriched") are more likely to report taking classes or doing crossword puzzles than individuals in Group 3 ("home + socially enriched"), who are more likely to report volunteering and membership in a church or other social group.

These qualitative differences are important for two reasons. First, these activities may influence cognitive and physical outcomes through different mechanistic pathways and thus may differ in their magnitude of effect on these outcomes. Second, and perhaps more importantly, these qualitative differences may suggest that individuals have unique motivations for staying active. This provides more information to leverage when targeting interventions to maintain or supplement current lifestyle activity engagement with the goal of preventing cognitive and physical declines. For example, if Group 3 (i.e., "home + socially enriched") is shown to have

better cognitive and physical trajectories than Group 1 (i.e., "home activities only"), then interventions targeting individuals in Group 1 may try to enrich their current lifestyle by offering these same activities within a social context, such as providing a book club or sewing group. Similarly, interventions targeting individuals in Group 3 ("home + socially enriched") could leverage their motivation to be socially engaged in new ways that may further benefit their health. The Experience Corps program is an example of a successful intervention that has taken this approach, where older individuals who are motivated by a generative desire to help future generations are encouraged to stay active through volunteering in a local school system (Fried et al., 2004).

This dissertation is, in part, a proof-of-concept of this novel method of characterizing heterogeneity in lifestyle engagement and examining whether these lifestyle engagement groups have different trajectories of cognitive and physical functioning.

The specific aims of this dissertation are (see Figure 1.3):

Aim 1a: Characterize lifestyle engagement groups in a sample of older adults using latent class analysis.

Hypothesis. We hypothesized that older adults group by activity type (e.g., intellectual vs. social) or activity setting (e.g., home vs. community). A prior nationally-representative study (Manalel et al., 2018) used a similar approach and found groups with different amounts and types of engagement, where those with the highest engagement reporting more social activities within the community. We hypothesized that those in classes reporting more activities (i.e., quantitative

differences) here also report different activity types that suggest different extrinsic and intrinsic motivations to be active.

Aim 1b: **Examine whether lifestyle engagement groups (Aim 1a) have differential risk of dementia incidence.**

Hypothesis. Groups with quantitative and qualitative differences differ in their risk of incident dementia. Lifestyle engagement groups characterized by high overall engagement or high engagement specifically in intellectual activities have the lowest risk (Scarmeas et al., 2001).

Aim 2: Examine longitudinal changes in domain-specific cognitive functioning across lifestyle engagement groups (Aim 1a).

Hypothesis. As predicted by the use-it-or-lose-it (i.e., enrichment) hypothesis (Hertzog et al., 2009; Hultsch et al., 1999a; Salthouse, 2006), groups with quantitative and qualitative differences in activity patterns differ in baseline cognitive outcomes and changes in cognition over time. The largest differences are for measures of attention and memory (Bielak, 2010; Herzog et al., 2008). Lifestyle engagement groups characterized by high overall engagement or high engagement specifically in intellectual activities have the highest baseline levels and reduced declines over time in these domains (Bielak, 2010; Carlson et al., 2012; Hultsch et al., 1999a).

Aim 3: Examine longitudinal changes in markers of mobility and physical frailty across lifestyle engagement groups (Aim 1a).

Hypothesis. Given that lifestyle activities likely engage neural mechanisms key for maintaining mobility and physical functioning (Rosso, Studenski, et al., 2013; Varma, Hausdorff, et al., 2016), groups with quantitative and qualitative differences in activity patterns differ in baseline physical functioning outcomes (e.g., walking speed, self-reported exhaustion) and changes in

these outcomes over time. Lifestyle engagement groups characterized by high overall engagement or high engagement specifically in social institutional activities within the community have lowest baseline risk of physical frailty criteria and mobility limitations, as well as attenuated risk trajectories of these outcomes over time (Buchman et al., 2009; Rosso, Taylor, et al., 2013).

Chapter 2: Background

2.1. Public Health Significance of Cognitive and Mobility Declines

Cognitive and mobility changes with age are contributors to decreased functional independence and increased mortality (Alzheimer's Association, 2019; Guralnik et al., 2000). Some cognitive and mobility changes occur normally with aging and do not result in functional impairments (Glass, 1998; Verhaeghen & Salthouse, 1997). Yet, the prevalence of neurodegenerative conditions, such as dementia due to Alzheimer's Disease (AD), and mobility disabilities is expected to increase with the changes in population demographics with the aging Baby-Boomer generation (Alzheimer's Association, 2019; Verghese et al., 2006). For example, AD prevalence is expected to more than triple by 2050, from approximately 5 million to 15 million individuals in the U.S. alone (Brookmeyer et al., 2018).

Given the public health significance of cognitive and mobility changes in older adulthood, yet lack of universally effective pharmacological treatments for these conditions (Alzheimer's Association, 2019; Varma, Hausdorff, et al., 2016), preventive interventions are needed that target modifiable risk factors contributing to these conditions. Importantly, aging-related cognitive and mobility changes are related via common underlying neural mechanisms (Rosso, Studenski, et al., 2013), suggesting interventions could potentially improve both cognition and mobility simultaneously if they target these shared mechanisms (Varma, Hausdorff, et al., 2016). One such modifiable factor may be lifestyle activities, which incorporate various degrees of physical, cognitive, and social engagement (Bielak, 2010; Carlson & Varma, 2015).

The sections below further elaborate on: 1) cognitive and mobility changes with aging and shared neural systems linking both conditions, and conclude with 2) examining lifestyle activities as a potential protective factor against cognitive and mobility changes. For this last section, I critically evaluate the literature on lifestyle activities, including current gaps and barriers in the field that will be addressed in this dissertation.

2.2. Cognitive Changes with Aging

There are both normative and neurodegenerative cognitive changes that can occur with aging (Figure 2.1). *Normative cognitive changes* are those that occur free of significant impairment or pathological accumulations. These typically include aging-related decreases in *fluid cognitive abilities* such as in the executive functioning domain (i.e., ability to plan, problem solve, shift attention, and have goal-directed behavior) (Verhaeghen & Salthouse, 1997). However, not all cognitive abilities decline with aging. *Crystalized abilities*, such as vocabulary knowledge, typically do not show the same magnitude of aging-related declines (Verhaeghen & Salthouse, 1997). Thus, most cognitive interventions targeting community-dwelling older adults tend to target fluid abilities.

Further evidence for these normative aging-related cognitive changes comes from the Seattle Longitudinal Study, which began in 1956 and is ongoing (Schaie & Willis, 2010). They found that while *crystallized* abilities like verbal comprehension were relatively preserved until later life (>65 years old), *fluid* abilities like verbal memory, executive functioning, and processing speed begin declining in mid-life (>40 years old), resulting in lower performance on these tasks relative to verbal comprehension in older age (Schaie et al., 2004). Yet, there are also important cohort differences to account for when conceptualizing “normative” cognitive change.

Those in earlier-born cohorts (born 1883-1913) in the Seattle Longitudinal Study had both lower baseline levels and steeper declines in several *fluid* abilities from ages 50 to 80 compared to later-born cohorts (born after 1914). These cohort differences emphasize the importance of either adjusting for baseline age or restricting the sample to a single cohort when studying cognitive aging. Both approaches are used in the Ginkgo Evaluation of Memory Study, the dataset used in this dissertation.

2.2.1. Brain changes with normative aging. Normative cognitive changes are accompanied by aging-related changes in structural brain measures (e.g., regional volume, thickness, shape). Older adults typically experience an annual 0.8-2 percent decline in cortical volume, with bilateral temporal regions having the largest declines (Jiang et al., 2014). Subcortical regions of the medial temporal lobe, including the hippocampus and entorhinal cortex, experience increased rates of atrophy with age (Jiang et al., 2014). The hippocampus and entorhinal cortices are important for episodic memory function, and are typically heavily atrophied in neurocognitive disorders like Alzheimer's Disease (see following section; Barnes et al., 2009; McKhann et al., 2011). These underlying brain changes are important, given their potential to influence not only cognitive performance, but also other functional behaviors like mobility. Mobility and the neural mechanisms linking cognition and mobility are described more in later sections.

In contrast to normative changes, neurodegenerative cognitive changes are those involving significant impairments in one or many cognitive domains that result in declines in independent functioning. *Mild Cognitive Impairment* (MCI), also known as *Mild Neurocognitive Disorder* (American Psychiatric Association, 2013), is often considered an intermediate stage

between normal cognitive functioning and dementia. Those with MCI may have impairments in one or more domains of cognition, but have largely preserved independent functioning except for more complex tasks (e.g., managing money) (M. S. Albert et al., 2011). In contrast, *dementia,* or *Major Neurocognitive Disorder* (American Psychiatric Association, 2013), is characterized by impairments in more basic activities of daily living (e.g., bathing, eating). The clinical course of dementia is often described as an "insidious onset" of cognitive impairment with "gradual progressive declines" (American Psychiatric Association, 2013), and typically involves impairments in multiple cognitive domains (McKhann et al., 2011). There are several dementia subtypes, with Alzheimer's Disease (AD) being the most prevalent (Alzheimer's Association, 2019). AD is characterized by impaired episodic memory performance and accumulation specific brain pathology, including cortical atrophy and accumulation of beta amyloid and tau tangles (M. S. Albert et al., 2011).

Given that many cognitive tests are sensitive to normative aging-related cognitive changes, diagnoses of MCI or dementia require knowledge of longitudinal cognitive changes and often consider other risk factors, such as family history of dementia or brain biomarkers (e.g., amyloid and tau accumulation; cortical atrophy; enlarged ventricles) (Albert et al., 2011; McKhann et al., 2011). Finally, it is important to emphasize that normative cognitive changes and accumulation of brain pathologies need not lead to neurodegenerative impairments (Stern, 2002). This suggests that intervention is possible during preclinical stages to potentially modify trajectories of cognitive aging, and this has been a focus of extensive preventive research (National Academies of Sciences, Engineering, and Medicine, 2017). The current dissertation will examine both domain-specific cognitive changes and risk of neurodegenerative impairments (i.e., dementia).

2.3. Mobility Changes with Aging and their Connections with Cognition

Mobility is defined as the ability of an individual to move about their environment (Rosso, Studenski, et al., 2013). Mobility declines with age are thought to represent an intermediate, preclinical stage of functional disability, preceding inability to perform activities of daily living like basic physical tasks, bathing, or toileting (Fried et al., 2000; Harris, Kovar, Suzman, Kleinman, & Feldman, 1989). Fried et al. (2000) found that among the 69% of women who reported no mobility difficulties at baseline in the Women's Health and Aging Study (WHAS), about 16% and 11% of these women reported difficulties walking 0.5 mile or climbing 10 steps, respectively, after only 18 months of follow-up. Furthermore, those with preclinical indicators of mobility declines, including self-reported task modification due to mobility constraints or performance changes on walking speed, had significantly higher odds of reporting mobility difficulties at follow-up. Thus, aging-related, preclinical mobility declines provide an important target to prevent future functional disability.

Although mobility is a broad umbrella term, the current dissertation will focus on lower-extremity mobility, including gait speed. *Gait* is the pattern of movement of the body during locomotion (Rosso, Studenski, et al., 2013). About 35% of adults over 70 have a gait abnormality (Verghese et al., 2006), and gait abnormalities can lead to significant mobility limitations, increased cognitive impairment (Verghese et al., 2002), reduced quality of life (Guralnik et al., 2000), and mortality (Studenski et al., 2011).

Mobility and cognition are also intimately related and share similar neural pathways. First, domain-specific cognitive abilities, including processing speed and executive functioning, are strongly correlated with gait in epidemiologic studies (Rosso, Studenski, et al., 2013). Gait

changes or abnormalities have also been predictive of cognitive declines and dementia (Rosso, Studenski, et al., 2013). Second, brain imaging studies suggest prefrontal, cingulate, parietal, putamen, and the cerebellum regions, as well as the connecting tracts between them, are important for maintaining mobility functioning (Holtzer et al., 2014). These regions are also active during tasks requiring cognitive-motor integration (e.g., complex walking tasks; Rosso et al., 2019). Finally, further evidence for the link between mobility and cognition comes from intervention studies. Neurocognitive interventions targeting motor learning and those providing electrical stimulation to frontal brain regions have been shown to improve gait in older adults (Varma, Hausdorff, et al., 2016).

Given the connection between mobility and cognition and their influence on well-being in later life, it is important to consider potential protective factors that act on similar etiologic pathways. One potential protective factor is lifestyle activity engagement, which may provide meaningful roles for older adults that encourage sustained cognitive-motor integration.

2.4. Mobility Limitations as a Contributor to Physical Frailty

Highly related to mobility in later life is the concept of physical frailty. Physical frailty is an aging-related clinical state of vulnerability during which an individual is at heightened risk of adverse health outcomes (e.g., institutionalization, falls) and mortality (Fried, Tangen, et al., 2001; Rockwood et al., 1999). Prior to the 2000s, physical frailty was often operationalized inconsistently and sometimes considered synonymous with disability or comorbidity (Fried, Tangen, et al., 2001). Efforts to standardize the operationalization of physical frailty has led to it being conceptualized in two different ways in the literature: 1) as an accumulation of medical,

functional, and social deficits (i.e., frailty index; Rockwood et al., 1999), and 2) as a biological syndrome (i.e., phenotypic frailty; Fried et al., 2001).

The frailty index approach was developed by Rockwood and colleagues, and measures an individual's number of deficits out of a broad list of possible deficits (Mitnitski et al., 2001, 2002; Rockwood et al., 1999). The number of deficits evaluated has varied across studies (i.e., 20 items in Mininski et al. (2002), vs. 92 items in Mininski et al. (2001)), but often includes a range of medical (e.g., history of diabetes, Parkinson's disease), behavioral (e.g., ADLs, IADLs), laboratory (e.g., blood glucose), and functional (e.g., mobility impairment) measures. Importantly, the frailty index considers frailty to be deficit-driven, but is agnostic to the types of deficits. In other words, the more accumulated deficits, regardless of type, the more likely a person is to be frail.

Parallel to the frailty index, Fried et al. (2001) developed the frailty phenotype, which is conceptualized as a syndrome related to age-associated biologic declines in energetics and physical reserves. The phenotype consists of five dimensions: 1) shrinking/sarcopenia, 2) weakness, 3) poor endurance/exhaustion, 4) slowness, and 5) low activity (Table 2.1). Those exhibiting at least 3 of the above criteria are considered frail (i.e., have reached a critical mass of the criteria), whereas those with 1 or 2 criteria may be pre-frail (Bandeen-Roche et al., 2006; Fried, Tangen, et al., 2001). The frailty phenotype is associated with further disability, falls, and other poor health outcomes through decreased physiologic reserves to manage stressors (Xue et al., 2019).

There are strengths and limitations to each of the above physical frailty definitions. First, the extensive list of deficits included in the index approach can be easily taken from medical

records and interchanged with other measures without substantial loss in predictive ability (Rockwood et al., 2007; Walston & Bandeen-Roche, 2015). In contrast, phenotypic frailty relies on fewer criteria, and requires specific functional measures (e.g., walking speed) that are not always interchangeable nor possible to obtain from medical records. Nevertheless, the frailty phenotype is based off a clear conceptual framework related to biological aging, allowing for the determination of potential etiologic pathways (Walston & Bandeen-Roche, 2015; Xue, 2011). In contrast, the large list of deficits included in frailty indices makes it difficult to pinpoint etiological mechanisms and determine whether they measure a biological aging process or a chronic disease state. For example, frailty indices often include measures of disability (e.g., ADL impairments) and mental health (e.g., depression), which are considered conceptually distinct from the underlying loss of energetics and physical reserve that characterizes the frailty phenotype (Fried, Tangen, et al., 2001). Yet, understanding the underlying etiology of physical frailty is critical, as this information could be used to inform interventions that mitigate onset or progression of the syndrome and ultimately prevent its associated poor health outcomes. For this reason, the remaining discussion on physical frailty in this dissertation will center around phenotypic frailty.

Mobility is both a key component and behavioral correlate of the frailty phenotype. Within the cycle of frailty (Fried, Tangen, et al., 2001; Xue, 2011), mobility limitations are characterized as slow walking speed and reduced physical activity resulting from sarcopenia and exhaustion. Mobility declines ultimately lead to lower energy expenditure, contributing cyclically to further muscle loss. Mobility declines may be detectable earlier in the onset of physical frailty than other criteria (Xue, Bandeen-Roche, et al., 2008; Xue, 2011). Xue et al. (2008) found that 76% of the women who were non-frail at baseline in WHAS II developed the

weakness, slowness, and low activity criteria before exhaustion and weight loss. Mobility limitations may therefore help identify individuals of increasing vulnerability in the early/intermediate stages of frailty development.

However, mobility has a complex relationship with physical frailty, given that it is not only a measure of physical capacity, but also manifests behaviorally through physical activity. These behaviors can be influenced by a variety of psychosocial (e.g., self-efficacy, social supports) or environmental (e.g., neighborhood walkability) factors that are conceptually distinct from phenotypic frailty (Bandeen-Roche et al., 2019; Rosso et al., 2011; Xue, Fried, et al., 2008). These factors may especially influence the "low activity" criterion of phenotypic frailty. Bandeen-Roche et al. (2019) hypothesize that several interventions reporting benefits for frailty may have been driven primarily by intervention-related behavioral changes in physical activity, rather than changes in the physiological underpinnings of frailty. As a result, they argued that frailty interventions should target its physiological mechanisms broadly rather than the individual criteria, to properly determine whether the intervention successfully prevents frailty or just masks its symptoms.

Nevertheless, the behavioral component of mobility and physical activity is still an important modifiable factor in prevention of physical frailty, especially early in its progression. Xue et al. (2008) examined the relationship between life-space mobility, defined as an individual's self-reported ability to move freely in their environment, and incident frailty in the WHAS I sample. In contrast to WHAS II, WHAS I consisted of the subset of women who were the most disabled at baseline. Accounting for frailty-free mortality as a competing risk, they found that women who reported leaving their neighborhood less than four times per week had

1.7 times the risk of incident frailty compared to those who reported leaving more than four times. Furthermore, they found that being confined to the home (i.e., severe life-space constriction) predicted frailty-free mortality, but not incident frailty (Xue, Fried, et al., 2008). They suggested that this may have been due to the infrequency of frailty assessments and rapid acceleration to death in this group, which likely resulted in some of the individuals being misclassified as frailty-free before their death occurred.

Importantly, the authors also emphasized how despite the substantial mobility, IADL, and ADL difficulties in WHAS I at baseline; these difficulties were not perfect predictors of lower life-space mobility. This suggests that some participants may have been able to compensate for these declines in physical capacity using either internal (e.g., using assistive devices) or external (e.g., social supports) strategies to maintain their life-space mobility (Xue, Fried, et al., 2008). This discrepancy between reported difficulties and reported activities has been found in other observational studies of older adults (Glass, 1998) and is described later in this dissertation. This discrepancy also likely extends to measures of lifestyle engagement obtained using activity inventories. In these inventories, the amount of engagement reported by an individual is likely dependent in part on similar external and internal compensatory strategies, making lifestyle engagement an important and potentially modifiable risk factor. However, to date there have been few studies linking lifestyle engagement with mobility outcomes (see Section 2.6.2). Furthermore, to my knowledge there have been no longitudinal studies linking these measures to phenotypic frailty criteria. Given how lifestyle engagement may be an important modifiable behavioral factor related to frailty risk, this gap is important to investigate further.

2.5. Lifestyle Activities as a Protective Factor against Cognitive and Mobility Declines in Later Life

Research on the connection between lifestyle activities and cognitive functioning and cognitive impairments has been of theoretical and empirical interest for several decades (Schooler, 1984). Given the scope of the literature, lifestyle activity engagement has been defined and measured in a variety of ways. I briefly review these definitions and measures as well as provide a definition for lifestyle engagement as presented in the current dissertation.

2.5.1. Definitions of lifestyle activities. Lifestyle activities have been defined in many ways in the literature. Some researchers conceptualize lifestyle activities as including occupation (Schooler, 1984), whereas others focus more on those performed outside of work (i.e., leisure activities) (Carlson et al., 2012; Wilson et al., 2002). Still others include Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs; Lawton & Brody, 1969) in measures of "self-maintenance" lifestyle activities (Hultsch et al., 1999a). One problem with this last approach is that ADLs and IADLs are typically used as markers of functional impairment, so including them with leisure activities in aggregate lifestyle activity measures may change the conceptual meaning of these measures, given that there is typically very little impairment in these activities in community-dwelling versus clinical samples of older adults (Lawton & Brody, 1969). For this dissertation, I define lifestyle activities as those performed outside of a formal occupation, not including ADLs and IADLs, and that place various levels of physical, cognitive, and social demands on individuals. This definition narrows the conceptual meaning of lifestyle and may provide more variance in resulting lifestyle activity measures for community-dwelling

older adults. I will also use this definition later when selecting activities to retain for the latent class analysis (Aim 1).

2.5.2. Measures of lifestyle activity engagement. Lifestyle activities have also been measured and operationalized in different ways, which in turn allows study of different aspects of engagement. Lifestyle activities are most commonly measured using self-reported inventories. The Victoria Longitudinal Study Activity Questionnaire (Hultsch et al., 1993) asks about frequency (1=never, 9=daily) of participation in 70 activities over the past two years. These activities are grouped into different subdomains, including physical (e.g., jogging, walking), social (e.g., visiting friends), self-maintenance (e.g., cooking, shopping), passive information processing (e.g., watching a sporting event), novel information processing (e.g., learning a language), and integrative information processing (e.g., driving a car). The Florida Cognitive Activities Scale (Schinka et al., 2005) is a 25-item scale measuring frequency (1=never, 6=daily) of engagement in common activities selected to be primarily "cognitive" (e.g., reading books, playing chess). The Lifestyle Activity Questionnaire (Carlson et al., 2012) is 23-item inventory that measures frequency of engagement in activities with varying degrees of cognitive, physical, and social demands (e.g., gardening outside, volunteering, etc.). This inventory is detailed later in the dissertation and in the Appendix. Other studies also use variations of the items included in these scales, such as the cognitive activity inventory used in the Rush Memory and Aging Project (Wilson et al., 2005), which has overlapping items with the Lifestyle Activity Questionnaire and the Florida Cognitive Activities Scale (e.g., reading books, doing crossword puzzles), but also assesses activity engagement at various life stages (e.g., childhood, adolescence, adulthood, etc.).

The above inventories all measure *frequency* of engagement in individual activities (Bielak, 2017). Participants typically respond indicating how often they perform each activity on a Likert scale, ranging from "never" to "every day." Responses to individual items are then summed or averaged to produce a composite *frequency* score, indicating the amount individuals participated in the included lifestyle activities. Some studies have first converted frequency items from a Likert scale to a day scale (e.g., from "every day" to "30 days per month") to make the unit change in aggregate *frequency* interpretable as a 1-day change (Carlson et al., 2012).

There have been several variations on *frequency* measures used in the literature. Many studies take a domain-centered perspective on activity frequency, where activities are grouped into subdomains (e.g., physical, intellectual, etc.) via either theoretical groupings (e.g., Parisi et al., 2012) or empirical factor analytic methods (e.g., Lennartsson & Silverstein, 2001). Other studies have examined frequency of activity engagement using daily diary (Bielak et al., 2017) and day reconstruction (Smith et al., 2014) methods. These methods are valuable due to their mitigation of recall bias, but also can be subject to temporal biases depending on when the activity is measured (e.g., weekday vs. weekend).

More recently developed measures attempt to capture other aspects of engagement that may predict important health outcomes. Carlson et al. (2012) applied a novel measure of activity *variety*, where frequency items are recoded as binary variables indicating whether the individual ever does the activity (i.e., yes/no) and then summed to produce a composite. This measure suggests that the number of activities reported, regardless of the frequency with which one participates in them, may have meaningful implications for health outcomes (Carlson et al., 2012). *Variety* of engagement has since been found predictive of several cognitive and brain

outcomes in later life (Chan et al., 2018; Moored et al., 2018). Another advantage of examining *variety* compared to *frequency* measures is that they may be less susceptible to recall bias, as they require less detailed knowledge of how often an activity is performed. This may be especially important when measuring activity engagement in older adult samples at risk of memory impairments (James, Boyle, Buchman, & Bennett, 2011), but it should be noted that retrospective recall of even early life activities has had high test-retest reliability (ICC>.80) in samples of community-dwelling older adults (Schreiber et al., 2016).

Furthermore, Bielak (2017) developed a novel measure of activity *characteristics*, given that it may be the perceived level of cognitive demand of the activity, rather than the activity itself, that is protective against cognitive declines. For the Activities Characteristics Questionnaire, participants report the frequency with which they complete activities with specific traits (e.g., solving a problem on your own, learning a new skill, etc.). For example, a participant who reported "taking a class" on the Lifestyle Activities Questionnaire or Florida Cognitive Activities Scale would report "actively listening to information" on the Activities Characteristics Questionnaire, and other activities with this trait include "listening to talk radio or TV news." Models including this measure along with standard frequency and daily dairy measures of activity engagement accounted for the most variance in cognition than each measure alone (Bielak, 2017). Surprisingly, activity *characteristics* measures consistently had a negative relationship with cognitive performance. This may suggest that greater reported time doing cognitively complex activities may be a proxy measure for everyday cognitive difficulties, as individuals who spend more time doing complex cognitive tasks may require more time to do the tasks properly. It is also unclear whether participants can accurately categorize their daily activities according to specific cognitive traits (e.g., what constitutes "actively" vs. "passively"

listening to information), as this is itself an executive functioning task and may be influenced by stress or other contextual factors. Nevertheless, Bielak (2017) introduces the importance of considering not only quantitative, but also qualitative differences in activities, as these characteristics may inform not only how the activities act on health outcomes, but also what motivates the individual to remain active.

2.6. Evidence for Lifestyle Activities as a Protective Factor.

Below I review the literature on lifestyle activities, mobility, and cognition. I also highlight studies with findings that informed the conceptual framework and methodology used in the current proposal.

2.6.1. Cognition. There have been numerous cross-sectional and some longitudinal studies that have examined the relationship between lifestyle activity engagement and cognitive outcomes, including performance on cognitive tasks and risk of dementia. Studies examining late-life activity engagement and cognitive performance simultaneously (Hill, Wahlin, Winblad, & Bäckman, 1995; Hultsch et al., 1993; Parisi et al., 2012; Wilson et al., 1999) suggest that individuals with greater frequency of engagement in lifestyle activities also have better cognitive functioning. However, cross-sectional studies are unable to determine the temporal relationship between lifestyle engagement and cognition, and are limited by the potential for reverse causation. In other words, individuals of higher cognitive ability are also likely to be healthy enough to be involved in more lifestyle activities. Prospective longitudinal studies can better establish the temporal relationship between current activity engagement and future cognitive changes (Salthouse, 2006).

Longitudinal studies have provided mixed evidence for the relationship between activity engagement and cognitive aging, potentially due to differences in measurement and design. The Victoria Longitudinal Study (VLS) examined the relationship between engagement in 64 lifestyle activities that were classified into six domains (Hultsch et al., 1999a). Using latent change models, they found that lifestyle activities requiring "novel information processing" predicted changes in cognition, mediated through changes in working memory performance. However, there were no relationships between social or physical activities and cognition, potentially because the amount of activities included in these groups was much smaller (i.e., 4 and 7 activities, respectively) than those in the novel processing domain. A cross-sectional study in a socio-demographic risk sample from the Baltimore Experience Corps Trial found similar relationships (Parisi et al., 2012). Intellectual, but not physical, activities were associated with better cognitive functioning at baseline, yet this study also had only 4 activities included in the physical domain. Taken together with the extensive literature on the benefits of physical activity and cognition in older adulthood (Carlson & Varma, 2015; Erickson et al., 2011; Voss et al., 2014), these results may suggest that a greater variety of activities is needed to reliably measure the "physical" activity domain. These findings also suggest that using a domain-agnostic, person-centered approach to examining activity patterns in this proposal may forgo issues in measurement precision due to categorizing a limited number of activities into smaller groups.

Using a domain-agnostic approach to quantifying activity *variety*, Carlson et al. (2012) found that increased activity variety was associated with an 8-11% reduced risk of verbal memory and global cognitive impairments across 9.5 years of follow-up in the WHAS II. Importantly, when *variety*, *frequency,* and level of cognitive challenge of the activities were included in the same model, *variety* appeared to be the best predictor of cognitive outcomes. This

suggests that it may be the diversity of activities, rather than the intensity of participation, that may be most beneficial to cognitive aging.

A recent study in the Lothian Birth Cohort examined activity engagement at different periods of the lifespan that was reported retrospectively in later life (Gow et al., 2017). They found that more leisure activities in midlife were associated with greater cognitive ability level in later life, and more physical activities in later life were associated with less cognitive declines. This study highlights the importance of taking a lifespan approach to examining lifestyle activity and suggests that lifespan involvement in activates that encourage a mix of physical, cognitive, and social enrichment may best promote cognitive health.

Other longitudinal studies confirm these findings (Bennett et al., 2014), but some offer mixed results (e.g., Bielak, Gerstorf, Anstey, & Luszcz, 2014). For example, Fratiglioni et al. (2004) performed a comprehensive review of the literature that included physical, cognitive, and social lifestyle factors. Five of seven studies of social networks, and six of seven studies of non-physical cognitive activities, found that these lifestyle factors were associated with better cognitive performance and lower cognitive declines.

2.6.1.1. Dementia. Several longitudinal studies have examined the link between lifestyle activities and risk of incident dementia. Early studies have focused on broadly-defined leisure activities (e.g., knitting or other hobbies, socializing with friends, etc.) (Scarmeas et al., 2001; Verghese et al., 2003a). Scarmeas et al. (2001) found that those with high leisure activity had a 38% reduced risk of AD, after adjusting for covariates. Verghese et al. (2003) found that a one-point increase in cognitive activity scores was associated with 7% reduced risk of dementia, but physical activity scores were not related to risk of dementia.

The Rush Memory and Aging Project (MAP) and Religious Orders Study (ROS) both examined whether cognitive activities, defined as activities requiring information processing but minimal physical and social engagement, were predictive of incident MCI or AD. They found that both past and current cognitive activities predicted incident MCI and AD in separate models, but that the effect of past activity was attenuated when including both past and current activity in the same models (Bennett et al., 2014; Wilson, Scherr, Schneider, Tang, & Bennett, 2007).

Social activities and social integration have also been linked to lower risk for dementia (Bennett et al., 2014; Fratiglioni et al., 2004). Fratiglioni et al. (2004) found that three of six studies included reported a positive association between larger social networks and reduced risk of dementia. Furthermore, a study in MAP found that while there was no main effect of social networks on cognition or brain pathology (i.e., amyloid load and tangle density), social networks moderated the relationship between pathology and cognition where presence of pathology had little effect on cognition for those with larger networks (Bennett et al., 2006).

Importantly, researchers highlight the concern for potential reverse causation in these findings, where prodromal dementia symptoms may influence activity participation (Fratiglioni et al., 2004). This suggests that studies should examine lagged effects of activity engagement on dementia risk, as is done in the current dissertation.

2.6.2. Mobility. In contrast to research involving cognitive outcomes, there has been less work on how lifestyle activities, as defined above, may relate to mobility trajectories. Many studies show a cross-sectional link between having better mobility function and higher activity engagement (Everard et al., 2000; Mendes de Leon et al., 2003; Rosso, Taylor, et al., 2013). As with cross-sectional studies of lifestyle activities and cognitive outcomes, a major limitation is

the potential for reverse causation, where those of higher mobility are also likely to be involved in more lifestyle activities.

There have been few longitudinal studies investigating the association between baseline lifestyle activity engagement and mobility over time. As with dementia, a majority of these analyses come from the same cohorts (e.g., MAP, Buchman et al., 2009; James et al., 2011), and to my knowledge only one study has examined objectively-measured, lower-extremity mobility (Buchman et al., 2009). In the MAP sample, Buchman et al. (2009) studied global motor function, as measured by 9 objective muscle strength tests (e.g., arm abduction and flexion) and 9 objective motor tasks (e.g., time to walk 2.4 meters), in 906 individuals with an average of 4.8 years of follow-up. They found that decreased frequency of social activity was associated with more rapid rates of decline in global motor functioning, and this effect was equal to that of being about 5 years older at baseline (Buchman et al., 2009). They also found that this relationship remained after controlling for relevant confounders, including physical and cognitive activity, depressive symptoms, and demographics. This suggests that late-life lifestyle activities that are social in nature may have an independent association with motor trajectories.

Another longitudinal study in the MAP examined the relationship between frequency of social activities and self-rated ADL disability and mobility (James, Boyle, Buchman, & Bennett, 2011). More frequent social activity was associated with reduced hazard of developing an ADL or motor disability. Unfortunately, as the authors acknowledge, the self-reported mobility measures may be subject to recall bias or same-source bias. Given the lack of longitudinal studies examining the relationship between lifestyle activities and objectively-measured motor

trajectories, more studies in well-characterized cohorts with extensive follow-up are needed to replicate these findings.

The lifestyle activity literature on mobility outcomes is further complicated by how researchers conceptualize "mobility." As discussed earlier, mobility in the current proposal is defined as objectively-measured (i.e., "performance-based") mobility function. Yet, some researchers use lifestyle activity engagement as a proxy measure for mobility functioning (e.g., Gagliardi et al., 2007). This may conflate two different types of functioning: 1) *experimental functioning* (i.e., "could do"), what older adults are capable of doing in highly controlled settings, and 2) *enacted functioning* (i.e., "do do"), what older adults actually report doing in everyday life (Glass, 1998). A key distinction between these two types of functioning is the context in which they occur, as some experimental tasks restrict use of compensatory strategies (e.g., mobility aids and external supports) that may be used to complete activities in daily life. While objectively-measured mobility likely represents *experimental functioning*, self-reported lifestyle activities more likely measure *enacted functioning*. Furthermore, objective mobility measures have been predictive of important health outcomes, such as ability to perform ADLs and mortality (Guralnik et al., 1994, 2000). Thus, given their conceptual differences and the importance of objectively-measured mobility for future health outcomes, whether self-reported lifestyle activity engagement predicts objectively-measured mobility remains an important research gap.

2.6.3. Mechanisms. Several primary (i.e., cognitive and social engagement) and secondary (i.e., structural and functional brain plasticity) mechanisms link lifestyle activity patterns to beneficial cognitive outcomes in later life (Figure 1.1).

2.6.3.1. Cognitive mechanisms. Schooler's (1984) environmental complexity hypothesis posits that the complexity of an individual's environment is determined by the magnitude of stimulus and overall demand it places on cognition. Complex environments expose the individual to diverse stimuli and novel experiences, as well as require more frequent complex decision making (Schooler, 1984). Thus, those who have a more complex environment that tasks their cognitive abilities may exhibit greater improvement or maintenance of these abilities than those exposed to less complex environments. Lifestyle activity patterns characterized by higher *variety* of activities may therefore buffer against cognitive aging through requiring individuals to navigate a complex environment (Carlson et al., 2012).

Relatedly, the "use-it-or-lose-it" hypothesis (Hertzog et al., 2009; Hultsch et al., 1999a; Salthouse, 2016) posits that engagement in activities may moderate aging-related declines in cognitive abilities through maintenance or enhancement of cognitive abilities (Ericsson & Chamess, 1994) or through provision of compensatory mechanisms (e.g., strategies; Dixon & Bäckman, 1995). This hypothesis is supported by the literature on *cognitive training.* Unlike lifestyle activities as defined in this proposal, *cognitive training* targets specific cognitive domains (e.g., memory, processing speed, etc.) by encouraging repeated practice on tasks that challenge these abilities (e.g., Kliegl, Smith, & Baltes, 1989) or through provision of strategies to mitigate declines in these abilities (e.g., Rebok et al., 2014). Cognitive training can also be performed in highly controlled settings using experimental study designs (e.g., randomized

controlled trials), which makes them well-suited for examining the mechanistic pathways by which cognitive engagement influences cognitive performance trajectories with aging.

Cognitive training studies (Baltes, 1987; Karbach & Verhaeghen, 2014; Kliegl et al., 1989) have shown that while older adults generally reach a performance asymptote earlier than younger adults, there is variability in this asymptote and older adults can still improve in performance after several training sessions. In other words, while older adults may have a reduced *reserve capacity*, their ability for behavioral *plasticity* is at least partially maintained (Kliegl et al., 1989). Thus, engagement in a variety of cognitively-challenging lifestyle activities, even beginning later in life, may similarly contribute to *plasticity* in cognitive abilities despite a reduced capacity for change.

Few experimental cognitive training studies link training-related changes to everyday functional outcomes, including those relating to mobility. The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study is one of few cognitive training studies to examine how cognitive training may influence self-maintenance functioning (i.e., IADLs) (Jobe et al., 2001). Participants were randomized to a processing speed, memory, or reasoning training intervention, and examined 10 years after enrollment (Rebok et al., 2014). Those in the processing speed and reasoning groups maintained their training effects, and all intervention groups had better IADL functioning than the control group. Importantly, those receiving booster training sessions demonstrated additional improvements in performance for the processing speed and reasoning groups (Rebok et al., 2014).

Despite the key differences between lifestyle engagement and cognitive training, findings from ACTIVE and other training studies suggest that engagement in cognitively-demanding

activities may benefit both cognitive and functional trajectories in later life. Lifestyle activities performed outside of experimental settings (e.g., attending classes) may elicit similar plasticity in cognitive performance with aging, although this likely depends heavily on the level of cognitive demand of the activities, which may further vary depending on individual differences (Bielak, 2010). Accounting for individual differences necessitates longitudinal examination of *within-person* changes in cognitive and mobility outcomes (Salthouse, 2006), as is done in this dissertation.

2.6.3.2. Social mechanisms. Participation in lifestyle activities may increase social ties and reinforce meaningful social roles (Berkman et al., 2000). Social ties and meaningful social roles in later life may buffer against cognitive and mobility declines by reducing loneliness and depressive symptoms (Glass et al., 2006). Increased social ties may also provide more opportunities for social interaction, which places additional demands on cognitive functioning (Carlson, 2011). Finally, social engagement that reinforces meaningful social roles may provide purpose in life (Boyle et al., 2010) that in turn promotes sustained activity engagement. For example, the Baltimore Experience Corps Trial (BECT) was an intensive volunteering intervention that placed older adults in meaningful roles within the Baltimore City schools (Fried et al., 2004). This intervention leveraged older adults' desires to give back to future generations (i.e., generativity) to encourage sustained activity. In summary, social pathways linking lifestyle engagement to cognitive and mobility outcomes may further serve as important motivational factors for remaining active.

2.6.3.3. Physical mechanisms. Participation in lifestyle activities provides opportunities for aerobic (e.g., increased walking) and anaerobic (e.g., resistance; muscle strength) exercise, both

of which are protective against cognitive (Carlson & Varma, 2015; Voss et al., 2014) and mobility (Pahor et al., 2014) declines in older age. Although physical exercise may act on health outcomes via improvements in cardiovascular fitness, increasing evidence suggests that other physical pathways likely mediate this relationship, as well (Carlson & Varma, 2015). Cerebral blood flow may be one mechanism, as reduced cerebral blood flow in older age is associated with increased risk of hypertension and AD pathology. Exercise also promotes freely available Brain Derived Neurotrophic Factor (BDNF), which binds to prefrontal and hippocampal brain regions and promotes neurogenesis and synaptogenesis.

2.6.3.4. Neural mechanisms. Ultimately, the different pathways listed above likely influence behavioral and clinical outcomes through altering brain structure and function (Figure 1). Lifestyle activities may buffer against accumulation of brain pathology (e.g., beta amyloid and tau deposition) through promotion of brain and cognitive reserve (Stern, 2009). Brain reserve (i.e., *passive* reserve) consists of changes to brain structure that allow individuals to better cope with pathology, such as larger brain size, more neurons, and improved synaptic connections. Cognitive reserve (i.e., *active* reserve) refers to changes in brain function, such as increased neural efficiency or compensatory activity that allow individuals to complete tasks despite increasing pathology.

In agreement with this hypothesis, participating in complex activities has been shown to have benefits for brain structure (Carlson et al., 2015; Draganski et al., 2004; Moored et al., 2018; Stern, 2009) and function (Carlson, Erickson, et al., 2009; McDonough et al., 2015; Stern, 2009). Yet, cognitive and social activity also likely influence cognitive and brain health through

independent pathways, as several studies have found significant associations between these types of engagement and cognitive functioning, regardless of level of pathology (Bennett et al., 2014).

2.7. Sex and Other Individual Differences in Activity and Risk of Cognitive and Mobility Impairments

Recently the National Institutes on Aging introduced a new framework to research and combat health disparities with aging (Hill, Pérez-Stable, Anderson, & Bernard, 2015). Impetus for this framework comes from a rich literature on population-level differences in health by *fundamental factors,* including age, sex, race, socioeconomic status, and others. Below I briefly review how these factors are likely associated with lifestyle activity engagement as well as increased risk for cognitive and mobility impairments in later life.

2.7.1. Sex. Women are at higher risk of cognitive and mobility impairments in later life than men (Fried et al., 2000; Fried, Kasper, Guralnik, & Simonsick, 1995; Wu et al., 2017). For example, Wu et al. (2017) compared several nationally-representative samples and found that although prevalence estimates of dementia generally decreased for men between the 1990s and 2000s, prevalence estimates for dementia in women remained stable. One potential explanation for this is that women have a higher average life expectancy than men, and they are thus more likely to develop dementia, since the risk of dementia increases with age (Alzheimer's Association, 2019). However, older women are also more likely to have lower educational attainment, to have not had a formal occupation, and are less likely to be physically active during leisure time (Azevedo et al., 2007). Each of these may increase risk of cognitive and mobility impairments in women via the mechanistic pathways (e.g., cognitive reserve, cardiovascular fitness) included above.

2.7.2. Race. African-Americans are at higher risk of dementia (Mayeda et al., 2016), potentially due to increased psychosocial risk factors (Zahodne et al., 2017). Women of racial and ethnic minorities are at higher risk of cardiovascular issues and mortality than white women (King et al., 2000; Parra-Medina et al., 2010).

There are also racial differences in lifestyle activity engagement. Wilson et al. (1999) found that African-Americans in MAP reported less frequent engagement in cognitive activities than white adults. Furthermore, Barnes et al. (2004) found that older African-Americans in the Chicago Health and Aging Project tended to report less social engagement than white older adults. This racial difference was stable over time, but it was attenuated for women after accounting for socioeconomic status (Barnes, Mendes de Leon, Bienias, & Evans, 2004). Further analyses revealed that activities associated with higher socioeconomic status, such as visiting a museum, were reported less by African-Americans in this sample.

Other research has shown that racial differences in social engagement may be attributable in part to differences in cultural context. For example, participation in church activities has been reported more frequently among African-Americans (Kim & McKenry, 1998), especially among older African-American women (Bowie et al., 2017). In contrast, white older adults are more likely to report involvement in formal organizations or volunteering (Kincade et al., 1996). Aside from increasing social ties, church participation has been associated with reduced depressive symptoms (Reese et al., 2012) among African-Americans, which may further protect against declines in cognition and mobility in later life.

2.7.3. Other socieodemographic differences. Age has been found to be related to amount (Buchman et al., 2014) and types (Verbrugge et al., 1996) of activities engaged in later

life. Education and other socioeconomic factors have been shown to be related to cognitive activity engagement (Chan et al., 2018; Wilson et al., 1999) and access to activities (King et al., 2000), specifically for older women of color.

2.7.4. Health differences. Chronic physical conditions like stroke, heart disease, diabetes, and other cardiovascular illnesses have been linked to limited activity engagement (Saunders et al., 2016) and increased risk for poor cognitive and mobility outcomes (Snyder et al., 2015). Furthermore, depressive symptoms in older adulthood increase risk of functional disabilities on activities of daily living (Gallo et al., 2003; Griffiths et al., 1987). This increased risk may be mediated in part by decreased cognitive performance on memory and problem-solving tasks (Gallo et al., 2003), as well as reduced social activity that may increase sedentary behavior (Glass et al., 2006).

Ultimately, since these individual differences relate to both lifestyle activity and the health outcomes included in this dissertation, they will be examined as potential confounders of the relationship between lifestyle activity patterns and health outcomes. A *confounder* is a variable associated with both an exposure and an outcome that, when not adjusted for, distorts the observed relationship between the exposure and the outcome (Porta, 2008). However, it is important to emphasize that these individual difference factors are more than just covariates to adjust for in models to isolate a mechanistic pathway, but that they also carry meaningful information about an individual's life context. Furthermore, research examining differences in activity engagement and health outcomes in groups most vulnerable, such as African-American women of low socioeconomic backgrounds, is much needed. A vast majority of epidemiologic

and intervention studies of older adults include samples that are mostly white and of higher education (Hill et al., 2015; Tzuang, Owusu, Spira, Albert, & Rebok, 2018).

2.8. Current Gaps in the Literature

Despite ongoing research on the relationship between late-life lifestyle activities and cognition and mobility, there remain several gaps in the literature that are addressed by this proposal. This proposal addresses these gaps within the conceptual framework developed in the prior section, and the aims are represented schematically in Figure 3.

2.8.1. Lack of data-driven approaches that integrate both amount and types of activity engagement. *Frequency* and *variety* measures have certain limitations that may be addressed by instead examining data-driven activity *patterns*. First, if we assume that the subset of activities included in activity inventories measure a construct of overall lifestyle engagement, these measures do not account for measurement error in that latent construct. Second, sum or average measures assume that lifestyle engagement is a purely dimensional construct, where groups of individuals are distinguished by the *amount* of activities they report.[1] This ignores the possibility that groups may report qualitatively different response *patterns* of activities. For example, a study in the Health and Retirement Study found that a latent group of older adults who endorsed more "diverse" activities (i.e., a larger *amount*), also endorsed more social activities performed outside the home (i.e., different response *patterns*) than those in the "restricted" class (Manalel et

[1] On the surface, this approach appears to parallel the Rockwood frailty index (Section 2.4), where frailty is conceptualized as the number of total deficits, regardless of the types of deficits. Yet, in their establishment of the concept of activity variety, Carlson et al. (2012) also accounted for differences in cognitive demand of specific types of activities by using weighted counts. The current latent class approach is similar, but instead groups individuals by the activities they have in common (i.e., person-centered approach), rather than grouping activities by level of cognitive demand (i.e., item-centered approach).

al., 2018). Using a latent class approach to grouping individuals with different patterns of activities can therefore incorporate both information related to *amount* of engagement indicated by frequency and variety measures, as well as provide additional context (e.g., shared *characteristics*; Bielak, 2017) about what constitutes and what may commonly motivate their activity. This information could be leveraged when tailoring interventions to promote sustained activity in different groups of older adults by promoting purpose in life (Boyle et al., 2010), an approach used by prior successful interventions (Fried et al., 2004; Parisi et al., 2007).

2.8.2. Lack of longitudinal studies of lifestyle engagement, characterized by activity response patterns, and the "use-it-or-lose-it" hypothesis. Although several longitudinal studies suggest aggregate lifestyle activity measures may buffer against cognitive declines, very few studies examine how groups grouped by amount and types of lifestyle activity engagement may experience different cognitive trajectories. Given that different activity measures have been shown to be predictive of different cognitive outcomes (Bielak, 2017), activity measures that capture multiple aspects of engagement may also be better suited to predict cognitive trajectories over time. To my knowledge, Manalel et al. (2018) is the only study to examine this relationship using a person-centered, latent class analysis, and they found that the classes differed only in intercept, but not slope, of memory performance over time. Thus, it remains unknown whether similar results would be found for measures of executive functioning or attention, two cognitive domains that are more sensitive to aging-related declines among community-dwelling older adults (Buckner, 2004) and sensitive to differences in activity engagement (Bielak, 2010).

Furthermore, there are limited prospective cohort studies available that have examined the temporal relationship between lifestyle activities and cognitive outcomes. Despite being well-

characterized with extensive follow-up, the MAP and ROS are limited by possible selection bias due to being enriched with individuals with a family history of dementia (Bennett et al., 2014). Therefore, replication of results found in these studies in other well-characterized samples remains an important future direction. Data in this proposal will draw from the Ginkgo Evaluation of Memory Study (Chapter 3), a randomized clinical trial examining the efficacy of ginkgo biloba supplements for preventing incident dementia in participants over the age of 75 (DeKosky et al., 2006). Given how the sample had to meet a relatively high level of baseline functioning to be included (Section 3.1.2), replicating results in this sample may provide important evidence for the value of lifestyle activity engagement among older adults during preclinical stages of disability.

2.8.3. Lack of longitudinal studies investigating lifestyle engagement and mobility and physical frailty outcomes. As previously mentioned, the scope of studies examining whether lifestyle engagement predicts objective mobility changes and physical frailty is limited. To my knowledge, this would be the first study to examine the relationship between lifestyle engagement, characterized using activity response patterns, and objective and perceived markers of physical frailty. Three points are worth reiterating for why this is an important gap in the literature. First, objective mobility performance and physical frailty are important preclinical outcomes, given they have been predictive of later independent functioning and mortality in older adults (Bandeen-Roche et al., 2006; Fried, Tangen, et al., 2001; Guralnik et al., 1994, 2000). If lifestyle engagement predicts objective mobility performance and markers of physical frailty, then this may provide additional evidence for how lifestyle activity may impact not only cognition, but also the well-being of older adults more broadly. Furthermore, answering this question may provide initial evidence for the role of mobility and physical frailty as mediators

between lifestyle engagement and incident disability, further elucidating the etiologic pathways by which lifestyle engagement impacts health in later life.

Second, examining how lifestyle engagement is associated with physical functioning trajectories is a natural extension upon the literature on lifestyle engagement and cognition. To reiterate, mobility and cognition share common neural pathways, and cognition plays an important role in executing proper movements (Rosso, Studenski, et al., 2013). Thus, lifestyle activity may also influence mobility in older adulthood through some of these shared pathways or through maintenance of cognitive functioning.

Finally, examining physical and cognitive outcomes simultaneously can be informative about the cognitive and physical demands of specific activity patterns. For example, given that lifestyle activities require varying degrees of physical and cognitive engagement, finding that certain groups with distinct activity patterns experience differential benefits of activity engagement on cognitive versus mobility trajectories would be informative about which activity groups are most protective for which outcomes. This may have implications for interventions, where groups with specific lifestyle activity patterns can be targeted with interventions aimed to supplement their current lifestyle.

3. Chapter 3: The Ginkgo Evaluation of Memory Study

All three aims of this dissertation use data from the Ginkgo Evaluation of Memory Study (GEM). GEM was a randomized-controlled trial conducted with community-dwelling older adults to examine the efficacy of ginkgo biloba supplements in preventing incident dementia (primary outcome), as well as cognitive declines and cardiovascular events (secondary outcomes ; DeKosky et al., 2006). Details about participant recruitment and the measures used in this dissertation are included in the sections below. Given that there was no effect of the ginkgo biloba treatment in the main trial and that the treatment intervention was not a primary focus of this dissertation, details regarding the administration and adherence to the supplement protocol are not included here, but can be found elsewhere (DeKosky et al., 2006, 2008). All studies were approved by their respective study site Institutional Review Boards. The secondary data analyses in this dissertation were approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

3.1. Participants

3.1.1. Recruitment. Initially, GEM aimed to recruit participants from the Cardiovascular Health Study (CHS; Fried et al., 1991), an existing prospective, population-based cohort study of community-dwelling older adults (Fitzpatrick et al., 2006). However, two-thirds of the eligible CHS participants refused to enroll after initial telephone screening, and CHS participants made up only about 10% of the final GEM sample. Therefore, most of the participants were newly recruited for GEM.

Recruitment occurred between September 2000 and June 2002 at four study sites: Hagerstown, Maryland (Johns Hopkins University); Pittsburgh, Pennsylvania (University of Pittsburgh); Winston-Salem and Greensboro, North Carolina (Wake Forest University), and

Sacramento, California (University of California –Davis). Methods of recruitment varied across study sites (Fitzpatrick et al., 2006), but the most effective approaches included mailing lists (e.g., voter registration, America List), on-site visits (e.g., retirement centers, community functions), and media advertisements (e.g., newspaper, television, radio).

3.1.2. Inclusion and exclusion criteria. Given that GEM was a clinical trial, there were numerous inclusion and exclusion criteria for enrollment. Eligible participants had no prevalent dementia, were at least 75 years of age, had English as their primary language, and could identify a proxy contact. The age criterion was relaxed for a small group of African American CHS participants who were between 71-75 years old. The proxy contact was critical due to concerns with anosoagnosia (i.e., lack of awareness of one's own cognitive deficits), and given that many functional or cognitive deficits are often noticed by a family member or friend before being reported by the participant (DeKosky et al., 2006). Proxy contacts were replaced if they were no longer willing to participate.

The complete list of exclusion criteria is included in Table 3 of DeKosky et al. (2006). These included taking medication contraindicated with use of Ginkgo Biloba supplements (e.g., warfarin, antipsychotics, tricyclic antidepressants, donepezil or similar medications for cognitive problems), extensive use of Vitamin E supplements (>400 IU/day), and refusal to stop use of over-the-counter Ginkgo Biloba supplements. Participants were also excluded if they had a history of bleeding disorders, Parkinson's Disease or taking dopaminergic receptor agonists, cancer within the past 5 years if it would inhibit their ability to participate, congestive heart failures with disability, or hospitalization for depression within the last year or Electroconvulsive Therapy (ECT) within the last ten years. There were also various exclusion criteria using a lab blood test (e.g., blood creatinine >2.0 mg/dL, B12 levels ≤210 pg/mL, etc.). Finally, participants

were excluded if they were currently participating in another prevention or treatment trial, currently participating in a clinical trial that could affect GEM outcomes, or if they had any condition that would inhibit full participation in GEM, at the discretion of the clinical study staff (DeKosky et al., 2006).

3.1.3. Study sample. There were 7,709 individuals screened for eligibility. There were 4,637 participants who were excluded, 2,149 for not meeting inclusion criteria and 2,488 for refusing to participate. There were 3,072 participants randomized into the two treatment arms (Ginkgo Biloba vs. placebo), but 3 participants in the placebo group were found to be ineligible after randomization due to prevalent dementia or Parkinson's Disease. The final study sample consisted of 3,069 participants, 1,545 in the intervention and 1,524 in the placebo group. Relatively few participants were lost to follow-up (97 in the intervention, 98 in the placebo group). For this dissertation, the final analytic sample included data from all 3,068 participants enrolled at baseline. One individual was removed due to lack of available Lifestyle Activity Questionnaire data (see below).

3.2. Study Procedure

The procedure for GEM is outlined in Figure 3.1. Participants were prescreened using the Telephone Interview for Cognitive Status (TICS) and those who passed and met the other above eligibility criteria were scheduled for a screening visit. During screening, participants were consented and were adjudicated for dementia according to the procedure described below in Section 3.3.2. Participants determined to have dementia were excluded. Participants who had normal cognition or Mild Cognitive Impairment proceeded to have a blood test, ADL/IADL assessment, depression screen, and an assessment of current medications and medical history. These participants were then scheduled for a baseline visit, which occurred at a median of 33

days after screening (*IQR*: 22-46). During the baseline visit, participants completed a physical assessment, neurological examination, functional assessment, health habits questionnaire, and were randomized to either the ginkgo biloba treatment or placebo control group. Participants returned approximately every 6 months to complete dementia screening, depression screening, updated medications and medical history, and ADL/IADL assessment (Figure 3.2). During annual assessments only, participants also had a functional assessment, which included measuring usual walking speed.

3.3. Measures

3.3.1. Lifestyle Activity Questionnaire (LAQ). As part of the health habits questionnaire, participants were asked the frequency with which they participated in 23 everyday activities (e.g., cooking, reading, gardening, etc.) over the past year on a 6-point Likert scale (0 = never/less than once a month, 5 = every day). Items were then re-coded as a binary (yes/no) variable indicating whether or not participants engaged in each activity at least once per month during the past year. This 1) mitigated potential problems with rarely endorsed response options resulting in sparseness in certain response patterns (Collins & Lanza, 2010), 2) made it easier to interpret resulting latent classes, and 3) mitigated potential recall bias by lessening cognitive demands required to recall precise frequency of activity engagement. The complete list of the 23 activities is included in Appendix 1.

3.3.2. Adjudication of Dementia and Mild Cognitive Impairment. Dementia was adjudicated by expert clinicians using the DSM-IV criteria (American Psychiatric Association, 2000), informed by results from a standardized GEM Study Neuropsychological Test Battery

(NTB), neurological exam, and a magnetic resonance imaging (MRI) scan (DeKosky et al., 2006).

Screening for incident dementia took place every 6 months for up to 8 years (Figure 3.3). Participants were administered the full NTB at that visit if they had a decrease in score on at least 2 of the 3 following tests: Modified Mini-Mental State Examination (3MSE; Teng & Chui, 1987), CDR (Morris, 1993), or the cognitive subscale of the Alzheimer's Disease Assessment Scale -Cognitive Subscale (ADAS-Cog; Mohs, 1996). Participants also received the full NTB at that visit if 1) they or their proxy reported a new memory or other cognitive problem, 2) dementia was diagnosed since the prior visit by their personal physician, or 3) they were prescribed a dementia-related medication (e.g., cholinesterase inhibitor).

Table 1 lists the tests included in the full NTB. These included the California Verbal Learning Test (CVLT) immediate and delayed recall (Delis et al., 1987), Modified Rey-Osterrieth Complex Figure copy and recall tasks (Becker et al., 1987; Osterrieth, 1944), Wechsler Adult Intelligence Scale – Revised (WAIS-R) Block Design (Wechsler, 1981), Boston Naming Test (Judith Saxton et al., 2000), Semantic Verbal Fluency (animals; Spreen & Strauss, 1998), Trail Making Test Parts A and B (Reitan, 1958), WAIS-R Digit Span Forwards and Backwards (Wechsler, 1981), Stroop Color-Word Test (Trenerry et al., 1989), the American National Adult Reading Test (AMNART; Nelson, 1982), and Raven's Colored Progressive Matrices (Raven, 1956).

Participants were sent for full adjudication if they had either: 1) abnormal scores on ≥5 tests, at least one being a memory test, and there were a higher number of impaired tests than at baseline, 2) abnormal scores on four tests, at least one being a memory test, there were a higher number of impaired tests than at baseline, and at least one test was incomplete, or 3) two

abnormal domain scores, with one being memory. Cut-points for "abnormal" scores were at 1.5 standard deviations below age- and education-stratified norms that were previously derived from the Cardiovascular Health Cognition Study (CHCS; Lopez et al., 2003). Pending cases were also identified and referred to the CDC neuropsychologist for review if the participants had either: 1) abnormal scores on three tests, at least one was in memory, and two or more tests were incomplete despite being successfully completed at baseline, or 2) abnormal scores on ≥5 tests, none were in memory and there were a higher number of impaired tests than at baseline (DeKosky et al., 2006). Review of pending case by the expert neuropsychologist allowed for better understanding of whether declines in test performance were due to cognitive impairment or other non-cognitive factors (e.g., sensory loss; DeKosky et al., 2006). The pending cases were then referred to the CDC for adjudication or returned for continued follow-up.

Full adjudication was performed by expert clinicians using data from the NTB, neurological exam, and MRI. The expert panel was blinded to treatment condition and consisted of two neurologists with expertise in dementia diagnosis, two neuropsychologists with expertise in cognitive assessment of dementia, and a psychometrician with expertise in scoring the CDR. Individuals classified as dementia cases by the NTB received a full neurological exam and MRI to confirm the participant met the clinical criteria. A final review of cases was performed by the GEM adjudication panel, which was also blinded to study condition and further included two certified radiologists to analyze the MRI according to a standard protocol. Ratings were made for cortical atrophy, white matter lesions, ventricular size, and number and size of brain infarcts.

Final diagnoses were assigned based on criteria from the 1) National Institute of Neurological and Communication Disorders and Stroke Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984), 2) Alzheimer's Disease

Diagnostic and Treatment Centers (ADDTC; Chui et al., 2000), and 3) National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN; Erkinjuntti, 1994; Rockwood et al., 1994). Participants were assigned to the following categories: 1) dementia of Alzheimer's type, 2) mixed Alzheimer's/vascular dementia (i.e., meeting both NINCDS and ADRDA criteria for AD and ADDTC criteria for possible/probable vascular dementia), 3) vascular dementia only, or 4) dementia, other etiology (e.g., Lewy-body dementia, etc.). Given the very low prevalence of vascular dementia (5%) in this sample, we did not use the dementia subtypes and instead used all-cause dementia as the main endpoint in subsequent analyses.

3.3.2.1. Mild Cognitive Impairment (MCI). MCI was adjudicated using a similar procedure as above, with some key differences. MCI was defined as meeting two criteria (Snitz, Saxton, et al., 2009): 1) a CDR global score of 0.5, and 2) scoring $\leq 10^{th}$ percentile on at least 2 of 10 neuropsychological test scores in memory, language, visuospatial abilities, attention, and executive function domains. Like the 1.5 standard deviation ($\sim 7^{th}$ percentile) cutoff used in the original dementia adjudication, the 10^{th} percentile cutoffs were based on normative data from the Cardiovascular Health Study (Lopez et al., 2003; Snitz, Saxton, et al., 2009). The 10^{th} percentile cutoffs were used instead to 1) account for how some cognitive tests were not normally distributed, making percentile rank cut-offs more appropriate, and 2) to provide a more sensitive cutoff for clinically-meaningful cognitive impairment (Snitz, Saxton, et al., 2009). Furthermore, the criterion for having a CDR score of 0.5 was crucial, as using the NTB criteria alone resulted in substantial overestimation the number of MCI cases at baseline (Snitz, Saxton, et al., 2009).

3.3.3. GEM Neuropsychological Test Battery (NTB)

The full GEM NTB included several standardized neuropsychological tests spanning multiple cognitive domains: memory, construction, language, attention/psychomotor speed, executive functioning, and intelligence (Table 1). Intelligence tests (i.e., National Adult Reading Test and Raven's Progressive Matrices) were administered during the baseline screening session only.

All remaining tests in the NTB were administered throughout the study in two scenarios: 1) diagnostic or 2) regular/non-diagnostic. First, the diagnostic NTB was administered if participants tripped the dementia screening algorithm during a six-month follow-up session as described in the dementia adjudication procedures (Section 3.3.2). Second, non-diagnostic NTB were administered to all participants regardless of whether they tripped the dementia screening algorithm starting in around 2004, the 6th year of data collection (3-4 years of study time for participants). Non-diagnostic NTB were then administered annually to all remaining participants without prevalent dementia. Details of each neuropsychological test are included in the following sections separated by domain.

3.3.3.1. Construction. The GEM NTB included two tests measuring visual perception and organization, as well as visual-motor coordination.

Block design. For the Wechsler Adult Intelligence Scale-Revised (WAIS-R) block design subtest, administrators present participants with a block pattern that they then need to replicate using blocks with one-color and two-color sides within a specific time-limit (Wechsler, 1981). Visuospatial construction scores on this task were the number of patterns that were correctly replicated within the time-limit (range: 0-24).

Rey-Osterrieth complex figure (copy condition). In this paper-pencil task, administrators present participants with an abstract, complex figure that they then need to replicate (Becker et

al., 1987; Osterrieth, 1944). The task is untimed and the stimulus image is not taken away until the task is ended. Visuospatial construction scores on this task were the total number of correct figure elements (e.g., specific lines with correct orientations), with partial credit given for distorted but properly placed elements, or vice versa (range: 0-24).

3.3.3.2. Memory. Two tests measuring verbal and visual episodic memory are included in the GEM NTB.

California Verbal Learning Test (CVLT). The CVLT is a word list learning task where participants are told sixteen common nouns over a series of five immediate recall trials (List A, Delis et al., 1987). The listed words belong to one of four semantic categories (i.e., spices/herbs, fruits, tools, clothing). After each trial, participants are asked to recall the words in any order. Participants are then given an interference list of sixteen words (List B), half of which belong to two of the same semantic categories from the original list (fruits and spices/herbs) and the other half belonging to two new categories (fish and kitchen utensils). Participants are then asked to freely recall the original list (List A) immediately after (i.e., short delayed recall) and after a 20-minute delay (i.e., long delayed recall). Verbal recognition is also tested after the short and long delay trials by first cuing participants with the four semantic categories.

Verbal learning is measured by summing the number of words recalled over the five immediate recall trials (range: 0-80). Verbal episodic memory is measured using the number of words recalled after the long delay (range: 0-16). Strategy use (e.g., semantic and serial clustering) during word learning has also been examined using this task (Stricker et al., 2002) and other list-learning tasks (Gross & Rebok, 2011), although is not a focus here.

Rey-Osterrieth complex figure (delayed recall). Participants are asked to replicate the same complex figure they were previously asked to copy after a 20-minute delay, during which

they do not see the stimulus image (Becker et al., 1987; Osterrieth, 1944). Visual memory scores on this task were the total number of correct figure elements (e.g., specific lines with correct orientations), with partial credit given for distorted but properly placed elements, or vice versa (range: 0-24).

3.3.3.3. Language. The GEM NTB included two tests measuring word retrieval and semantic verbal fluency.

Boston Naming Test. Participants were presented with 30 images that they then needed to verbally name (Judith Saxton et al., 2000). If the participant could not freely provide the correct name, a semantic cue was provided, followed by a phonemic cue if needed. Word retrieval scores consisted of the number of names correctly freely recalled (range: 0-30).

Controlled Ordered Word Association Test (COWAT). Participants were given a specified letter (e.g., "F") and asked to name as many words that started with that letter within one minute, excluding proper nouns, numbers, or words that end in a different suffix (Spreen & Strauss, 1998). Phonemic verbal fluency scores were the number of correct, non-duplicated words provided within the time limit.

In a follow-up task, participants were given a category (e.g., animals) and asked to name as many words that belonged in the category as they could within one minute (Spreen & Strauss, 1998). Semantic verbal fluency scores were the number of correct, non-duplicated words provided within the time limit.

3.3.3.4. Attention/psychomotor speed. One task was used to measure attention and psychomotor speed.

Trail-Making test (Part A). The Trail-Making Task Part A (TMT-A) asks participants to connect a sequence of randomly scattered numbers in order without lifting their pencil (Army

International Test Battery, 1944; Reitan, 1958). Participants were timed and given a maximum of 3 minutes to complete the task. Time to complete the TMT-A was used as a measure of psychomotor speed.

Digit span forwards. The Wechsler Digit Span forwards task (DSF) is a measure of attention (Wechsler, 1987). The participant is read aloud a list of numbers that they must repeat in the same order. The task stops after the participant makes errors on two consecutive lists of the same size. Attention scores were the number of correct trials (range: 0-14).

3.3.3.5. Executive functioning. Three subdomains of executive functioning were included in the GEM NTB due to their high sensitivity to aging-related changes in older adults (Buckner, 2004): 1) task-switching, 2) working memory, and 3) inhibition.

Trail-Making Test (Part B). Part B of the TMT (TMT-B) asks participants to connect a randomly scattered sequence of numbers and letters in ascending order (i.e., 1, A, 2, B, etc.) without lifting their pencil (Army International Test Battery, 1944; Reitan, 1958). Participants were timed and given a maximum of 6 minutes to complete the task. Time to complete TMT-B, adjusting for time to complete TMT-A, was used as a measure of task-switching.

Digit span backwards. The Wechsler Digit Span backwards task (DSB) is a measure of working memory span (Wechsler, 1987), and directly follows the DSF task. The participant is read aloud a list of numbers that they must repeat in backwards order. The task stops after the participant makes errors on two consecutive lists of the same size. Working memory scores were the number of correct trials (range: 0-14).

Stroop color-word task. Participants were presented sequentially with two stimulus cards containing the names of colors (e.g., blue) that were printed in ink of a different color (incongruent, e.g., “blue” printed in red ink; Trenerry et al., 1989). For the first card, participants

were asked to say the names of each printed word as fast and as accurately as they could in two minutes (e.g., without mistakenly saying the ink color instead of the printed word on incongruent trials). For the second card, participants had to say the name of the color ink as fast and accurately as they could in two minutes. The number of correct colors named on the second trial was used as a measure of inhibitory ability (i.e., the Stroop effect).

3.3.3.6. Intelligence. Two tests were included at baseline to measure premorbid word knowledge and fluid intelligence.

National Adult Reading Test – American version (AMNART). For the AMNART, participants read aloud a list of 45 words that cannot be phonetically pronounced (Nelson, 1982). Correct pronunciation is thought to correspond with prior knowledge of the word, capturing an individual's vocabulary knowledge. Vocabulary scores consisted of the number of incorrect words.

Raven's progressive matrices. Participants were presented with an 3x3 matrix of abstract geometric patterns with a missing section (Raven, 1956). They are then asked to determine from a list of options which piece of the image was missing. The task was completed in three sets of 12 matrices (i.e., "A," "AB," and "B"), with the matrices becoming progressively more challenging as the set went on. Set A tested primarily pattern completion and the remaining sets included more complex analogy problems. Total score across the sets (range: 0-36) was used as a measure of fluid intelligence.

3.3.4. Mobility and physical frailty outcomes (Aim 3). The following mobility outcomes were included to capture various domains of physical frailty. Some measures were consistent with the original CHS operationalization of the frailty phenotype (e.g., exhaustion,

slow walking), while others were derived from the available GEM data (e.g., weakness). Furthermore, given that only select criteria were measured longitudinally, we examined trajectories of the individual frailty criteria over time, rather than the phenotype.

3.3.4.1. Slow Walking Speed. Participants were asked to walk for 15 feet on a standardized, straight course at their usual pace. They could use a cane or any necessary walking aids during the task. Their time (sec.) to walk the course was recorded at 3 feet and 15 feet markers. Sex- and height-specific cutoffs were used to identify individuals with slow gait (Fried, Tangen, et al., 2001). These cutoffs were originally used to identify those at or below the 20th percentile of usual gait speed in CHS. Individuals with slow gait included: 1) men with height ≤173 cm and time ≥7 seconds, 2) men with height >173 cm and time ≥6 seconds, 3) women with height ≤159 cm and time ≥7 seconds, 4) women with height >159 cm and time ≥6 seconds.

3.3.4.2. Exhaustion. Two self-reported measures of perceived physical exhaustion were used in this study. The first was derived from the Fried et al. (2001) frailty criteria for exhaustion using two items from the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). These items included "I felt that everything I did was an effort" and "I could not get going." Individuals who reported experiencing either of these symptoms at least a "moderate amount of time" during the past week were categorized as having exhaustion.

We also derived a second measure of exhaustion using used four items from the Maastricht Vital Exhaustion Questionnaire (Appels et al., 1987). The full questionnaire was originally developed to identify those at risk for myocardial infarction (Appels & Mulder, 1988), and has been shown to also predict other cardiovascular outcomes, including coronary artery disease (Kopp et al., 1998) and novel cardiac events after surgery (Kop et al., 1994). Participants were asked whether they recently experienced any of the following: "often feel tired," "ever

wake up with a feeling of exhaustion or fatigue," "feel weak all over," and "have the feeling that you could not cope with everyday problems as well as you used to." Participants reporting at least two of the four items were categorized as having exhaustion. Prevalence of CES-D exhaustion and Maastricht Vital Exhaustion were used as separate outcomes in Aim 3.

3.3.4.3. Weakness. There were no longitudinal measurements of grip strength available in GEM. Therefore, we adapted a measure of self-reported difficulties with gripping, which had been shown to be a valid proxy for objectively-measured grip strength (Liu et al., submitted). Participants were asked: "Do you have any difficulty gripping with your hands?" Those responding "yes" were categorized as having grip weakness, and prevalence of grip weakness was used as an outcome measure in Aim 3.

3.3.5. Covariates.

Several covariates were adjusted for in analyses given their potential confounding of the relationship between lifestyle engagement and cognitive, physical, and dementia outcomes.

3.3.5.1. Demographics. Baseline age (years), race (white/non-white), and education (years) wereincluded as demographic covariates. Age has been found to be related to amount (Buchman et al., 2014) and types (Verbrugge et al., 1996) of activities engaged in later life. Furthermore, African-Americans are at higher risk of dementia (Mayeda et al., 2016), potentially due to increased psychosocial risk factors (Zahodne et al., 2017). Women of racial and ethnic minorities are at higher risk of cardiovascular issues and mortality than white women (King et al., 2000; Parra-Medina et al., 2010) and less likely to be involved in cognitively challenging activities (Wilson et al., 1999). Finally, education and other socioeconomic factors have been shown to be related to cognitive activity engagement (Chan et al., 2018; Wilson et al., 1999) and access to activities (King et al., 2000), specifically for older women of color.

3.3.5.2. Medical comorbidities. Total number of medical comorbidities at baseline was also included as a covariate, given that these conditions may limit activity engagement (Saunders et al., 2016) and increase risk for poor cognitive and mobility outcomes (Snyder et al., 2015). The self-reported comorbidities included hypertension, current/former smoking, diabetes, acute myocardial infarction, heart failure, atrial fibrillation, stroke, and transient ischemic attack.

3.3.5.3. Depressive symptoms. A modified 10-item CES-D was used to measure baseline depressive symptoms (Appendix 2). Items were measured on a 4-point Likert scale (0 = rarely/none of the time, 1 = some/little of the time, 2 = moderate amount of time, 3 = most of the time). Responses were summed to produce a composite depressive symptom score, and scores ≥10 were identified as potential clinical depression (Björgvinsson et al., 2013). Depressive symptoms in older adults have been linked to reduced social activity (Glass et al., 2006) and increased risk for poor cognitive and mobility outcomes (Gallo et al., 2003; Griffiths et al., 1987).

Chapter 4: Risk of Dementia Differs across Lifestyle Engagement Groups: A Latent Class and Time to Event Analysis in Community-Dwelling Older Adults

With increasing active life expectancies post-retirement (Crimmins et al., 2016), older adulthood brings about novel chances for lifestyle activity engagement. This potential for new or renewed engagement in everyday physical, cognitive, and social activities has been suggested as one way to prevent cognitive declines and impairments in later life (National Academies of Sciences, Engineering, and Medicine, 2017). To that end, several studies have found that self-reported lifestyle activities are protective against incident dementia (Bennett et al., 2014; Scarmeas et al., 2001; Verghese et al., 2003b; Wilson et al., 2007). Yet, it remains unclear which aspects of activities (e.g., amount or type) are most predictive, how to best measure these factors, and how to use them to inform interventions. The current study uses both established and novel approaches to characterize lifestyle engagement groups that may be relevant for future interventions, and examined their risk for dementia incidence over a median of 6 years.

4.1 Quantifying Activity Variety to Capture Lifestyle Engagement

Engagement in a larger array of enriching activities in later life, also called activity *variety*, is thought to be directly related to complexity of one's lifestyle (Carlson et al., 2012). Activity *variety* is typically operationalized as a count (Chan et al., 2018; Moored et al., 2018; Scarmeas et al., 2001) or weighted-count (e.g., weighted by level of cognitive demand; Carlson et al., 2012) of self-reported activities done during a specific period (e.g., past year). The conceptual basis for the benefits of activity variety draws from the environmental complexity (Schooler, 1984), enrichment (Hertzog et al., 2009), and cognitive reserve hypotheses (Stern, 2002), which together posit that more enriched environment engagement (i.e., higher number of activities) may promote structural and functional neurocognitive changes to maintain cognitive

functioning with age and protect against dementia-related pathology (e.g., amyloid plaques and neurofibrillary tangles).

Research using *variety* measures has found that the number of activities endorsed, regardless of the frequency with which one participates in them, may have meaningful implications for mitigating neurocognitive impairments in later life (Carlson et al., 2012; Chan et al., 2018; Moored et al., 2018; Podewils et al., 2005; Scarmeas et al., 2001). Scarmeas et al. (2001) measured self-reported counts of 13 leisure activities (e.g., going to classes), and found that there was an 11% reduction in risk of dementia for each additional leisure activity reported. Notably, this inventory also included activities commonly considered to be "passive" and less cognitively-enriching (Parisi et al., 2012), such as watching TV and listening to the radio. Furthermore, Carlson et al. (2012) used a count score weighted by the cognitive intensity of the activities to capture activity variety, and found that increased variety was associated with an 8-11% reduction in risk of verbal memory and global cognitive impairments across 9.5 years of follow-up.

We sought to expand upon these findings in a novel sample well-powered for examining risk factors for incident dementia (DeKosky et al., 2006), focusing on engagement in a larger range of specifically cognitively-, socially-, and physically-demanding (i.e., "active") activities. We hypothesized that those with a higher variety of these activities have reduced risk of dementia over time, independently of several demographic and health confounders.

4.2 Activity Subtypes Differentially Predict Dementia Risk

To study the benefits of activities that draw on specific functions (e.g., social, cognitive, etc.), researchers typically categorize activities into domains, either using *a priori* classification (e.g., Hultsch, Hertzog, Small, & Dixon, 1999), cognitive intensity weighting (e.g., Carlson et

al., 2012) or factor analytic (e.g., Lennartsson & Silverstein, 2001) methods. These approaches are important for identifying specific activity types that are most protective against cognitive declines and neurocognitive impairments.

Specifically, activities categorized as physically- (e.g., moderate exercise), cognitively- (e.g., taking courses), or socially-demanding (e.g., volunteering) have been shown to be associated with reduced risk for dementia (Bennett et al., 2014; Fratiglioni et al., 2004). For example, Hultsch et al. (1999) classified the 64 activities included in the Victoria Longitudinal Study of Aging into six domains, and found that only activities requiring "novel information processing" predicted changes in cognition, mediated through changes in working memory performance. Other studies have also found that specifically cognitively-demanding activities have the largest benefit for maintenance of cognitive function or prevention of cognitive impairments with aging (Bielak et al., 2014; Carlson et al., 2012; Scarmeas et al., 2001; Verghese et al., 2003; Wilson et al., 2007).

4.3 Linking Number and Types of Activities to Capture Lifestyle Engagement: A Latent Class Approach

Expanding upon the prior literature, the current study employs a novel latent class approach to characterize lifestyle engagement groups using both number and type of activities. Latent class analysis (LCA) is a person-centered approach where individuals are partitioned into unobserved groups, which are inferred based on persons' response patterns to a series of indicators (Collins & Lanza, 2010). Importantly, by grouping individuals by their response patterns, rather than activity count, LCA may better characterize lifestyle engagement variation by specifying which types, rather than just number, of activities are endorsed by individuals who have different levels of lifestyle engagement. We hypothesized that individuals would group by

specific activity types as defined by the prior literature (e.g., intellectual vs. social activities; Carlson et al., 2012; Hultsch et al., 1999; Parisi et al., 2012). Sociodemographic, health, and psychosocial factors also contribute to later-life differences in life-space mobility (Allman et al., 2006; Baker et al., 2003), defined as the spatial area in which individuals move in daily life (e.g., home, neighborhood, town, etc.), which could in turn dictate the settings in which they are active. Thus, we also hypothesized that individuals would group by activity setting, such as home-based (e.g., playing cards) versus community-based activities (e.g., volunteering).

An LCA approach may be especially relevant for intervention research, as it could suggest common motivations and settings in which individuals are active. These factors have been previously leveraged in prior intervention studies seeking to reduce cognitive declines and impairments with age (Fried et al., 2013; Parisi et al., 2007). For example, the Baltimore Experience Corps trial was an intergenerational volunteering program where older adults performed various supportive roles in local schools (Fried et al., 2013). This study recruited individuals motivated by a desire to volunteer and give back to prior generations (i.e., generativity) to encourage physical and cognitive engagement in later life. The current approach may reveal similar groups of individuals active in specific settings or activities relevant for further health-promoting interventions.

Current Study

The purpose of this study was twofold. First, we examined whether activity variety (i.e., activity count) predicted dementia risk after adjusting for relevant confounders. Confounders included variables hypothesized to be related to both activity engagement and dementia risk; and included age (Buchman et al., 2014; Verbrugge et al., 1996), sex (Azevedo et al., 2007; Wu et al., 2017), race (Mayeda et al., 2016; Zahodne et al., 2017), education (Chan et al., 2018; King et

al., 2000; Wilson et al., 1999), medical comorbidities (Saunders et al., 2016; Snyder et al., 2015), and depressive symptoms (Glass et al., 2006; Griffiths et al., 1987). We also examined potential effect modification by prevalent Mild Cognitive Impairment.

Second, we examined whether using a data-driven, LCA approach similarly predicted dementia risk and provided additional benefit in terms of understanding qualitative differences in activity patterns without sacrificing model fit. Better understanding the types of activities driving group differences in engagement may inform about which settings are relevant for intervention and in what ways individuals are motivated to be active.

4.4 Methods

Participants

Participants were volunteers from the Ginkgo Evaluation of Memory (GEM) study, a randomized clinical trial testing the efficacy of *Ginkgo biloba* supplements for preventing all-cause dementia (DeKosky et al., 2006, 2008). Recruitment occurred between September 2000 and June 2002 at four study sites: Hagerstown, Maryland (Johns Hopkins University); Pittsburgh, Pennsylvania (University of Pittsburgh); Winston-Salem and Greensboro, North Carolina (Wake Forest University), and Sacramento, California (University of California – Davis).

To be eligible, participants had to identify a proxy willing to be interviewed at each 6-month study visit. Individuals were excluded if they met either of the following criteria for prevalent dementia: 1) a diagnosis of dementia in the *Diagnostic and Statistical Manual for Mental Disorders IV* (DSM-IV) (American Psychiatric Association, 2000), or 2) a score >0.5 on the Clinical Dementia Rating scale (Morris, 1993). However, individuals with mild cognitive impairment (MCI) were included (Snitz et al., 2009).

Finally, those taking certain medications (e.g., warfarin, cholinesterase inhibitors), supplements (e.g., >400-IU vitamin E), or with a history of certain medical conditions (e.g., Parkinson's disease) were also excluded. Details regarding the eligibility requirements, recruitment procedures, and intervention (e.g., *Ginkgo Biloba* formulation) are found elsewhere (DeKosky et al., 2006). Data collection ended in April 2008. There were 3,069 individuals who met eligibility requirements and were assessed at baseline. One individual was missing responses for all items of the Lifestyle Activity Questionnaire, so 3,068 individuals were included in the analysis.

Measures

Before randomization into the original intervention or control group, eligible participants completed an extensive survey battery and functional assessment at baseline measuring their demographic and health characteristics.

Lifestyle Activity Questionnaire (LAQ). Participants were asked the frequency with which they participated in 26 everyday activities (e.g., cooking, reading, gardening, etc.) over the past year on a 6-point Likert scale (0 = never/less than once a month, 5 = every day). Items were re-coded as a binary (yes/no) variable indicating whether or not participants engaged in each activity at least once per month during the past year. This was done both to capture variety of activities (Carlson et al., 2012), rather than frequency, and to reduce sparseness of response patterns due to multiple response options.

Activity measures. Lifestyle activity was operationalized in two ways. First, we summed the number of endorsed activities into a count score, which has previously been used to quantify activity *variety* (Carlson et al., 2012). Second, we used a latent class analysis (LCA) approach to group individuals by both quantity and types of activity engagement. For the second approach,

using binary (yes/no) activity items versus the original frequency scale 1) mitigates potential problems with rarely endorsed response options resulting in sparseness in certain response patterns (Collins & Lanza, 2010), 2) makes it easier to interpret resulting latent classes, and 3) mitigates potential recall bias by lessening cognitive demands required to recall precise frequency of activity engagement.

Selecting activities. A potential concern with conducting an LCA with an activity inventory is that including many indicators may contribute to sparseness of response patterns. make model estimation difficult, and make unreliable adjudication of the number of classes (Collins & Lanza, 2010). To mitigate this, we used several criteria to select activities *a priori* to include in the final model: 1) *empirical*: removing activities endorsed by more than 90% or less than 10% of the sample, as these activities do not provide substantial variance for model estimation, and 2) *theoretical*: removing ADLs and IADLs (e.g., cooking) and activities previously identified as "passive" (e.g., listening to the radio; Parisi et al., 2015) to generate latent classes that conceptually capture differences in leisure activities requiring active engagement. This resulted in a final group of 18 activities (Table 1), which included activities from the remaining "physical," "intellectual/creative," and "social" domains. We conducted sensitivity analyses including the "passive" activities, and the results are reported in supplemental tables.

Dementia adjudication. Details regarding the adjudication of incident dementia diagnoses has been described in Chapter 3.3.2 of this dissertation and elsewhere (DeKosky et al., 2006, 2008). In brief, screening for dementia occurred every six months and adjudication was performed if participants had either: 1) abnormal scores on ≥5 tests on the GEM Study Neuropsychological Test Battery (NTB; Table 3.1), at least one being a memory test, and there were a higher number

of impaired tests than at baseline, 2) abnormal scores on four tests, at least one being a memory test, there were a higher number of impaired tests than at baseline, and at least one test was incomplete, or 3) two abnormal domain scores, with one being memory. Cut-points for abnormal test scores were derived from normative data from the Cardiovascular Health Study (CHS; Lopez et al., 2003). Adjudication was performed by a panel of expert clinicians using the DSM-IV criteria for dementia (American Psychiatric Association, 2000), informed by results from the GEM Study NTB, neurological exam, and an magnetic resonance imaging (MRI) scan (DeKosky et al., 2006).

Descriptive Covariates. Several measures were used to explore demographic and health differences between the activity classes.

Demographics. Baseline demographic variables included age (years), race (white/non-white), education (years), and study site (Hagerstown, Pittsburgh, Sacramento, Winston-Salem/Greensboro).

Medical Comorbidities. Participants reported their current medical comorbidities and risk factors. These included self-reported hypertension, current/former smoking, diabetes, acute myocardial infarction, heart failure, atrial fibrillation, stroke, and transient ischemic attack. A sum count of each binary (yes/no) response to these variables was generated to measure total medical comorbidities.

Mental health.

Depressive symptoms. A modified 10-item Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) was used to measure depressive symptoms (Appendix 2). Items were measured on a 4-point Likert scale (0 = rarely/none of the time, 3 = most of the time). Responses were summed to produce a composite depressive symptom score, and scores ≥10

were identified as potential clinical depression (Björgvinsson et al., 2013). For participants where at least one item was refused or missing, person-mean imputation was conducted where missing/refused items were replaced with the mean score on the completed items before computing the final score (Downey & King, 1998). This technique does not artificially reduce variability between individuals like item-mean imputation and provides adequate reliability estimates when the number of participants with missing responses in the sample is small (Downey & King, 1998). Imputation was only used for the 2.0% (n=60) of participants with missing CES-D responses.

Mild Cognitive Impairment (MCI). As stated previously, individuals with MCI were included in the current sample. MCI was defined as meeting two criteria (Snitz, Saxton, et al., 2009): 1) a CDR global score of 0.5, and 2) scoring ≤10th percentile on at least 2 of 10 neuropsychological test scores in memory, language, visuospatial abilities, attention, and executive function domains. The 10th percentile cutoffs were based on normative data from the Cardiovascular Health Study (Lopez et al., 2003; Snitz, Saxton, et al., 2009).

Analytic Strategy

Tabulations and summary statistics (e.g., means, standard deviations) were generated to compare covariates across activity variety sum scores and activity classes. Both activity variety and activity classes were included as predictors in separate hierarchical time to dementia analyses (see Step 3 below). For the LCA, a multistep approach was used to enumerate (Step 1) and assign (Step 2) individuals to the classes before conducting the time to dementia analyses (Step 3).

Step 1: Latent class enumeration. Class enumeration was determined by fitting a series of models of increasing number of classes. To account for the large number of indicators

included, and to assess the degree to which the enumeration process was sensitive to the specific activities included, we first conducted repeated latent class analyses using 10 semi-random subsets of 9 of the 18 activities (4 intellectual, 1 physical, 4 social). Model fit was evaluated using the lowest Bayesian Information Criterion (BIC) and a significant Bootstrapped Likelihood Ratio Test (BLRT). The BLRT test compares the improvement in fit between a *k* class model and a *k*-1 class model, and the BIC and BLRT tend to perform better than other model-selection criteria in simulation studies (e.g., Akaike's Information Criteria, Lo-Mendell-Rubin test) (Nylund et al., 2007). The criterion for a significant BLRT test was set to α=.001, given the potential for overfitting due to the high number of indicators included given our sample size (Dziak et al., 2014). Using a lower BIC and significant BLRT as the selection criteria (Nylund et al., 2007), a 3- to 5-class solution was generally the best fit across these subsets of activities. Notably, for some activity subsets, the 5-class models had did not converge due to sparse response patterns, in which case a 4-class model was chosen (see Supplemental materials, Appendix 3).

After evaluating the fit of the models with activity subsets, we fit a full model using all 18 activities and examined the theoretical interpretability of the 3-, 4-, and 5-class solutions (Collins & Lanza, 2010). A model with fewer classes that captured distinct activity groupings (e.g., social vs. intellectual; home-based vs. community-based) that adhered to our *a priori* hypotheses was favored over a model with more classes that had significant overlap with existing classes or appeared to be distinguished almost entirely by engagement in a single activity.

Step 2: Class assignment. After class enumeration, class assignment was done using two methods: 1) modal class assignment, where individuals are assigned to the class with the highest posterior probability, and 2) using the Vermunt (2010) 3-step approach. The former method has

been found to have less downward-bias of the associations between latent class and the outcome when compared to other posterior-probability based assignment methods (e.g., pseudo-class assignment; Lanza et al., 2013). The Vermunt (2010) method is a modification of the approach by Bolck, Croon, and Hagenaars et al. (2004), where weights for individual participants are used as training variables to assign them to latent classes. This approach is thought to better account for potential error due to misclassification and may produce estimates with less downward-bias compared to posterior-probability-based approaches (Lanza, Tan, et al., 2013; Vermunt, 2010).

Step 3: Time to dementia analysis. We then used activity variety and class assignment as predictors in separate hierarchical discrete time proportional hazards analyses of time to dementia onset. Complementary log-log regressions were used to estimate the hazard ratios for each predictor. The baseline evaluation session was used as the study entry time. Study exit occurred at either the time of dementia onset, time of death, or the time of last contact for the study. Time was included as discrete indicators (visits 1-15). The proportional hazards assumption was explored using time-specific (i.e., predictor*time) terms for each predictor (Royston & Lambert, 2011), and any predictors in violation were examined in stratified analyses. Model 1 included only the activity variety score or activity class indicators. Model 2 was adjusted for demographic and health variables, including treatment group (intervention vs. control), study site, baseline age, sex, race, education category, depression (CES-D≥10), and medical comorbidities. To flexibly model the association between baseline age and incident dementia, we included spline terms for each 5-year interval of baseline age (i.e., >80, >85, >90) to allow for a nonlinear relationship. Importantly, we hypothesized that individuals with prevalent MCI may have attenuated associations between activity class and dementia compared

to those with normal cognition at baseline. Thus, Model 3 further stratified by MCI status, to examine whether association between activity class and dementia risk differed by MCI status.

To compare the predictive utility of the activity variety sum score versus the lifestyle engagement groups, we generated Receiver Operating Characteristic (ROC) curves for each model and compared their respective Area Under the Curves (AUCs; Zweig & Campbell, 1993). AUCs indicate the extent to which the included variables discriminate between those who did and did not have incident dementia, with a higher AUC representing better discrimination.

Sensitivity analyses. Occasionally latent class analyses can yield classes where certain covariate ranges are not observed (i.e., "non-positivity"), rendering simple covariate adjustment insufficient (Collins & Lanza, 2010). We therefore generated propensity scores using a multinomial logistic regressions of modal class assignment on the covariates to further examine the covariate spread across classes (Lanza, Coffman, et al., 2013).

4.5 Results

Sample Characteristics

Descriptive statistics for the current sample are presented in Table 4.2. The sample had an average baseline age of 78.5 (SD=3.3), was mostly white (95%), and had an approximately even sex distribution (53% male). Most participants were highly educated, with only 36% having a high school degree or less. About half of participants rated their health as "very good" or "excellent," few had significant depressive symptoms (7%), and most had few medical comorbidities (*M*=1.4, *SD*=1.1). Participants reported about 9 activities, on average (*SD*=3.0, range: [0,18]). "Reading books" was the most frequently reported (83%), while "drawing and painting" was the least reported (11%; Table 4.1).

Latent Class Analysis

Class enumeration. To account for the large number of indicators used and to assess the degree to which the enumeration process was sensitive to the specific activities included, we conducted latent class analyses using 10 semi-random subsets of 9 of the 18 activities (4 intellectual, 1 physical, 4 social). Using a lower BIC and significant BLRT as the selection criteria, a 3- to 5-class solution was generally the best fit across these subsets of activities. Notably, for some activity subsets, the 5-class models had convergence issues due to sparse response patterns, in which case a 4-class model was chosen (see Supplemental materials, Appendix 3). Table 4.3 presents the class enumeration results (step 1) for 2-, 3-, 4-, 5-, and 6-class models for the full set of 18 items. A 4-class model was chosen based on the two criteria mentioned previously. The 4-class model has a significant BLRT ($p<.001$) and lower BIC than the 2- and 3-class solutions, suggesting that the 4-class model fit better than those models. While the 5-class model had improved fit statistics (significant BLRT, lower BIC) compared to the 4-class model, there was little gain in theoretical interpretability by including a fifth class (see "Class structure" below). Table 4.3 should be interpreted cautiously in light of the potential for overfitting with the full set of items and our sample size, hence our emphasis on interpretability taken together with adjudication of formal criteria in activity subsets as described above.

Class structure. Figure 4.1 is a plot of the item-response probabilities of activity engagement by latent class for the 4-class model. Importantly, there were not only differences in amount of activities by class, but also differences in types of activities chosen across classes. Class 1 (Social Intellectual; n=662, 22%) had high probabilities of engagement broadly across intellectual and social activities. Class 2 (Intellectual; n=514, 18%) had high likelihood of engagement in most intellectual (e.g., viewing art, computer use) and some social activities (e.g.,

movies), but less so in social institutional activities (e.g., volunteering, social clubs, church). In contrast, Class 3 (Social; n=1,036, 32%) had high probabilities of engagement in social institutional activities, but was less likely to report intellectual activities. Finally, Class 4 (Least Active; n=856, 28%) had lower probabilities of engagement in most intellectual and social activities compared to the other classes. Yet, their probabilities of engagement in some home-based activities, such as doing crossword puzzles or playing cards, were comparable to Class 3, suggesting that the main difference between these two classes may be their engagement in social institutional activities. There were little differences across classes in the two physical activities included (i.e., "gardening," "walking").

Comparison to 3- and 5-class structures. Figure 4.2 includes plots of the item-response probabilities of activity engagement by latent class for the 3- and 5-class models. The 3-class model was highly similar in structure to Classes 1 (Social Intellectual), 3 (Social), and 4 (Least Active) in the 4-class model. The primary difference between the 3- and 4-class models was the addition of Class 2 (Intellectual), which primarily split off from Class 1 (Social Intellectual). Comparing Class 1 in both models, the addition of Class 2 led to slight increases in item-response probabilities for social institutional activities (e.g., volunteering, church) in Class 1. This further supports the characterization of Class 2 as a less social but intellectually-active group.

The 5-class model had an additional group (Class 5) that was similar in structure to the Intellectual (Class 2) and Social (Class 3) groups in the 4-class model, but was less likely to report social institutional activities. The differences in intellectual activities between these classes were inconsistent. For example, Class 5 had a higher likelihood of engagement in "drawing" and "sewing" compared to Class 2 (Intellectual), but less likelihood for "taking

courses," "viewing art," and "using computers." We did not have any *a priori* hypotheses suggesting groups would differ on these specific activities. Furthermore, the large overlap in the confidence intervals for the item-response probabilities between this class and others in the 5-class model made it difficult to discern whether these estimates were meaningfully different and whether Class 5 was a truly distinct group. Therefore, we selected the 4-class model for subsequent analyses.

Time to Dementia Analyses

Tables 4.4 and 4.5 present unadjusted and adjusted discrete time proportional hazards models for activity variety and lifestyle engagement classes on time to dementia diagnosis from study entry. There was a median of 6.0 years of follow up (IQR: [4.9, 6.5]). Only MCI status was in violation of the proportional hazards assumption, so we included models stratifying by MCI status (Model 3).

Activity variety predicting dementia risk. Each additional activity reported was associated with 8.4% reduced hazards of dementia (Table 4, Model 1). This association was slightly attenuated but still significant (HR=.933, 95% CI:[.91,.96], p<.001), after adjusting for demographic and health covariates. Stratifying by MCI (Model 3) revealed that lower activity variety was significantly associated with higher dementia risk for those without MCI (HR=.936, CI:[.91,.96], p=.001), but not those with MCI (HR=1.01, CI:[.96,1.06], p=.808).

Lifestyle engagement groups predicting dementia risk. Compared to individuals in the Social Intellectual group (Class 1), individuals in the Social group had a 33% increased hazards (95% CI:[1.04,1.70], p=.024) and individuals in the Least Active group (Class 3) had a 66% increased hazards (95% CI:[1.29,2.41], p<.001) of dementia over time (Table 5, Model 1; Figure 2). Only the association for the Least Active group was still significant (HR=1.55, CI:[1.2,2.1],

p=.001) after adjusting for demographic and health covariates. Stratifying by MCI status (Model 5) revealed that the Least Active group had a higher dementia risk compared to the Social Intellectual group for those without MCI (HR=1.49, CI:[1.08,2.08], p=.017), but not those with MCI (HR=1.04, CI:[.67,1.61], p=.862). There was no difference in hazards of dementia between the Social Intellectual and Intellectual groups in any model (p's>.05).

Comparing model fit indices. The AUCs comparing the adjusted models of activity variety count (AUC=.741) and lifestyle engagement groups (AUC=.742) suggested that both variables provided relatively the same discrimination of dementia status (Supplemental Figure 4.1). This implies that using our data-driven LCA approach did not add to the predictive utility of using a simpler count measure of activity engagement. However, it suggests that the LCA approach also did not result in a substantial loss of model fit when compared to the established sum score approach.

Sensitivity analyses.

Using the Vermunt (2010) approach yielded similar results to using modal class assignment (Supplemental Table 2). The Social group no longer had a significant difference in hazards of dementia compared to the Social Intellectual group in the unadjusted model (HR=1.40, 95% CI:[.98,2.01], p=.066). The Least Active group (Class 4) had a higher risk of incident dementia compared to the Social Intellectual group in both the unadjusted (HR=1.82, CI:[1.33,2.50], p<.001) and adjusted models (HR=1.73, CI:[1.23,2.44], p=.002). Stratifying the analysis by MCI status revealed that this association was maintained for those without baseline MCI only (HR=1.64, CI:[1.07,2.53], p=.024).

Examining the propensity scores for each class revealed some variation in covariate ranges for the Social Intellectual (Class 1), Social (Class 3), and Least Active groups (Class 4).

We therefore conducted a sensitivity analysis eliminating individuals with scores outside the range that was consistent across classes (Supplemental Figure 4.2). Individuals with Class 1 propensity scores >.52 or <.04, Class 3 scores <.16, or Class 4 scores >.60 were removed (n=59, 13 dementia cases). Removing these individuals did not change the prior findings (Supplemental Table 4.2).

4.6 Discussion

To our knowledge, this study is among the first to combine the use of traditional activity variety metrics with a latent class approach to characterize qualitative (e.g., type) differences in lifestyle engagement. Using the traditional count score, we found that lower activity variety was associated with higher risk of incident dementia over the seven-year study period, for those without baseline MCI. This association remained significant after adjusting for several relevant confounders. These findings agree with prior work suggesting that higher activity variety, especially for intellectual activities, is protective against aging-related cognitive impairments (Carlson et al., 2012; Scarmeas et al., 2001).

Several potential mechanisms may explain the relationship between activity variety and dementia risk. Engagement in a higher variety of activities may buffer against cognitive impairments through requiring individuals to navigate a complex environment, leading to greater utilization and maintenance of cognitive abilities (Schooler, 1984). Similarly, the enrichment hypothesis (Hertzog et al., 2009) posits that engagement in diverse activities may moderate neurocognitive impairments through maintenance or enhancement of cognitive abilities or through provision of compensatory mechanisms. Although research to date has found limited evidence for a direct relationship between activity engagement and dementia-related biomarkers (e.g., amyloid plagues and tau tangles; Bennett et al., 2014; Wilson & Bennett, 2003), higher

activity variety may also buffer against accumulated pathologies through structural (e.g., grey matter volume) and functional (e.g., functional connectivity) brain changes (Stern, 2002). To better clarify whether activity engagement may influence dementia risk through maintaining cognitive functioning with age, aim 2 of this dissertation examines the relationship between the current lifestyle engagement groups and domain-specific cognitive performance.

We found that a 4-class model adequately represented group differences in activity response patterns. As hypothesized, these patterns were distinguished by differences in amount, types (e.g., intellectual vs. social), and settings (e.g., home-based vs. community-based) of engagement. The Social Intellectual group (Class 1) had high likelihood of participation broadly in intellectual and social activities. The Intellectual group (Class 2) had higher probability of reporting most intellectual and some social leisure activities (e.g., movies) compared to the Social (Class 3) and Least Active (Class 4) groups. The Social group had high likelihood of participation in community-based social institutional activities (e.g., attending church, volunteering). Finally, the Least Active group had relatively less likelihood of engagement in intellectual and social activities overall, but still demonstrated high engagement in certain independent activities (e.g., reading books).

Findings using the LCA approach to predict dementia risk largely paralleled those from using activity variety, where individuals belonging to the Least Active group had the highest risk of incident dementia. This relationship remained for those without prevalent MCI after adjusting for several confounders. Those groups with high intellectual engagement (Social Intellectual and Intellectual) had the lowest risk of incident dementia, suggesting that those engaged in intellectual activities into later life are likely the best equipped to mitigate incident cognitive impairment. This agrees with the enrichment hypothesis (Hertzog et al., 2009), which suggests

that high intellectual engagement in later-life is not only associated with greater existing brain and cognitive reserves (Stern, 2002) that could delay impairment, but also actively attenuates future declines. Other studies have also found that high intellectual engagement is particularly protective against dementia (Scarmeas et al., 2001).

Both the activity variety and lifestyle engagement group predictors had similar AUCs and thus demonstrated similar performance in discriminating future dementia cases. This suggests that the quantitative difference in amount of activities may be primarily driving the protective relationship between lifestyle engagement and dementia risk, and that using a sum score to capture variety of engagement may be the simplest method to use when developing predictive models of dementia incidence. Importantly, however, using the LCA approach did not result in a loss of predictive utility when compared to a simpler sum score, even despite potential losses in statistical power from categorizing individuals into only four groups.

Furthermore, the LCA approach provided additional information to characterize lifestyle engagement and which group-specific activities may be driving the association between variety and dementia risk. For instance, we found two groups of individuals that were more likely to participate in intellectual activities (i.e., Social Intellectual and Intellectual). These groups differed in their level of social institutional engagement, but had a similar risk of incident dementia. In agreement with the enrichment hypothesis (Hertzog et al., 2009), this may suggest that engagement in specifically cognitively-demanding activities may be especially protective against dementia. Other studies have found that more frequent engagement in specifically intellectual or cognitively-demanding activities appears to have the greatest protective benefit compared to other activity types (Hultsch et al., 1999b; Scarmeas et al., 2001).

Our person-centered LCA approach also did not rely on *a priori* specification of activity domains. This was especially important for revealing the qualitative differences in social institutional engagement between the groups, where those in Social Intellectual group had a high likelihood of participating in most social activities, but those in Social group had a high likelihood of engaging primarily in social institutional activities (e.g., church). This splitting of social activities into leisure and institutional subdomains is not typically done in research using activity frequency or variety measures (Hultsch et al., 1999b; Parisi et al., 2012; Scarmeas et al., 2001).

However, this difference between social leisure and social institutional activities is important, as it could suggest important contextual differences in social engagement between the groups that are relevant to preventing cognitive impairments. Given that the Social Intellectual and Intellectual groups were more likely to endorse going to movies, concerts, or plays; they may be of higher socioeconomic status (SES) compared to the other groups. Supporting this, the Social Intellectual and Intellectual groups were also more likely to be better educated than those in the Social and Least Active groups. Individuals with higher SES may have the necessary resources to maintain an active lifestyle that buffers against dementia-related pathology (Stern, 2002). Alternatively, additional social leisure activities may be associated with having a larger social network (Fratiglioni et al., 2004), expanded life space (James, Boyle, Buchman, Barnes, et al., 2011), increased physical activity (Najar et al., 2019; Ströhle et al., 2015; Voss et al., 2014), or additional cognitive stimulation related to novel environmental experiences (e.g., attending new concerts and encountering new individuals). Nevertheless, while we adjusted for education as a proxy of SES, future research using additional SES measures (e.g., wealth) with a similar LCA approach would help determine whether SES or social activity patterns is driving this

protective association with dementia. Past research adjusting for additional lifetime SES measures has found that activity engagement is independently associated with dementia risk (Chan et al., 2018; Wilson et al., 2007).

Finally, the lifestyle engagement groups presented here may also be useful for planning future interventions. While differences in number of activities may be important for determining an individual's lifestyle engagement (Carlson et al., 2012), further information on the qualitative differences in types of engagement may help pinpoint novel settings and behaviors to target. The Intellectual group, for example, may be more motivated to participate in a cognitively-intensive intervention, such as the Senior Odyssey, where participants work together to solve complex problems involving critical thinking and creativity (Parisi et al., 2007). In contrast, the Social group may be more motivated to participate in an intervention tied to social engagement or nested within a social institution, such as their church or social club. Supporting this, the Social Intellectual and Social groups shared similar a similar activity profile to BECT participants, who generally had high volunteerism and church participation and thus were likely more motivated to participate in the BECT intervention (Parisi et al., 2012). Integrating new interventions into existing activity contexts may ultimately promote more sustainable behavioral changes relevant to dementia prevention, by directly linking the intervention with engagement that already gives individuals purpose in life (Boyle et al., 2010).

There are limitations to the current study. First, we used a retrospective, self-reported inventory to measure activity engagement, which may result in recall bias. We attempted to mitigate recall bias by only using dichotomous (yes/no) activity responses that did not require recall of precise frequencies of engagement. Second, the activities included here are not exhaustive, and we did not include all of the LAQ items in a single LCA model to prevent issues

with model estimability (Collins & Lanza, 2010). Yet, we removed activities based on a clear empirical and theoretical rationale, and sensitivity analyses that included additional activities did not differ substantially in item-response probability patterns for the 4-class model. Finally, our sample was mostly white participants in a clinical trial, and the current findings warrant further replication and measurement invariance testing in more diverse samples.

The current study also had several strengths. We used a well-characterized sample of adults at higher age-related risk of cognitive impairment. Our sample had a median follow-up of 6 years, and was well-powered to detect differences in time-to-dementia analyses (DeKosky et al., 2006). Dementia was also adjudicated by expert clinicians using converging evidence from neuropsychological testing, neurological exams, and MRI (DeKosky, 2008; Snitz, Saxton, et al., 2009). Finally, our novel application of a person-centered LCA approach demonstrated that individuals group naturally by both amount and types of activities, and revealed qualitative differences in engagement that could imply potential motivational differences for staying active in later life. Our study is the first, to our knowledge, to use this approach to predict dementia incidence.

4.7 Conclusion

Increasing active life expectancies after retirement provide novel opportunities for encouraging lifestyle engagement in later life. The question remains as to how to quantify lifestyle engagement in a way that is useful both for predicting relevant health outcomes and for deploying health-related interventions. The current findings suggest that participating in a variety of activities in later life, regardless of frequency, appears to protect against incident dementia. We further found that individuals group naturally by both quantitative and qualitative differences in activity engagement, and these groups have differential risk of incident dementia. The

qualitative differences presented here indicate that individuals have different intrinsic or extrinsic motivations to remain active in later life. These motivational differences may provide one pathway for designing sustainable interventions that can be integrated into an individual's existing activity context to promote neurocognitive health in later life.

Chapter 5: Higher Lifestyle Engagement Predicts Higher Baseline and Attenuated Declines in Global and Domain-Specific Cognition (Aim 2)

Increasing active life expectancy post-retirement (Crimmins et al., 2016) offers novel chances for lifestyle activity engagement in older adulthood. This potential for new or renewed engagement in everyday physical, cognitive, and social activities has been suggested as one way to prevent later-life cognitive impairments (National Academies of Sciences, Engineering, and Medicine, 2017). Aim 1 of this dissertation found that risk of dementia differs across lifestyle engagement groups that differ in quantity and type of self-reported activities. Yet, even in the absence of clinical impairments, lifestyle engagement may have important benefits for later-life cognitive functioning. Furthermore, examining specific cognitive domains may provide additional insight into the mechanistic pathways by which lifestyle engagement prevents cognitive impairment in later life. The current study uses the novel application of a person-centered, latent class approach introduced in Aim 1 to characterize lifestyle engagement groups that may be relevant for future interventions, and examines differences in global and domain-specific cognitive trajectories over approximately 4 years of follow-up.

5.1 Lifestyle Engagement and Cognition: A Reciprocal Relationship

Lifestyle engagement is often operationalized as the total count or weighted-count of self-reported activities (i.e., activity variety; Carlson et al., 2012; Chan et al., 2018). Greater lifestyle engagement is thought to expose individuals to a more cognitively-demanding environment (Hertzog et al., 2009; Schooler, 1984). This may potentially protect against cognitive declines by promoting structural and functional brain changes or mitigating brain pathology (e.g., amyloid plaques and neurofibrillary tangles; Stern, 2002).

Important to the notion that lifestyle engagement may be neuroprotective is the need to account for the reciprocal relationship cross-sectionally between activity engagement and cognition (Bielak et al., 2012; Salthouse, 2006). This has been a concern in studies of clinical impairments (e.g., MCI, dementia) with limited follow-up (e.g., 1-3 years) (Salthouse, 2006; Verghese et al., 2003b). Reduced participation in activities at baseline among those with incident dementia may be attributable in part to preclinical cognitive declines, which occur gradually before onset of clinical impairments (Verghese et al., 2003b). In contrast, if the neurocognitive enrichment from activity engagement contributes to maintenance of cognitive functioning with age, then there should be differences in the rate of cognitive change over time by level of activity engagement (Salthouse, 2006). Testing these hypotheses requires a longitudinal design with sufficient follow-up time in the life course to rule out reverse causation driven by cross-sectional associations. The current study leverages over seven years of cognitive data from the Ginkgo Evaluation of Memory Trial (GEM), providing adequate follow-up time to test whether activity engagement is associated with rate of change in cognition.

Several prospective studies using self-reported activity measures have found differences in cognition at baseline but not in rate of cognitive change (Bielak et al., 2012; Gow et al., 2014, 2017; Hultsch et al., 1999b). Bielak and colleagues (2012) reported that neither between-person nor within-person variance in engagement in 16 activities were associated with changes in memory, executive functioning, perceptual speed, or vocabulary. Similarly, Gow and colleagues (2014) reported that leisure activity was associated with level of cognitive performance, but not with 10-year changes in cognition in the Glostrup 1914 Cohort. A study of the Lothian Birth Cohort reported that midlife social and intellectual engagement was associated with baseline cognition in older adulthood, but not with change over time (Gow et al., 2017).

Yet, other studies have reported the amount of activity reported during later adulthood may attenuate concurrent cognitive decline (Bielak et al., 2007; Carlson et al., 2012; Gow et al., 2017; Hultsch et al., 1999; Verghese et al., 2003; Wilson et al., 2002). Carlson and colleagues (2012) reported that increased variety in lifestyle activities during later life is associated with an 8-11% reduction in risk of verbal memory and global cognitive impairments across 9.5 years of follow-up in older women. Verghese and colleagues (2003) reported that individuals with more cognitive activities at baseline had reduced rates of decline in episodic memory. Notably, these studies included adults who were mostly over 70 years of age. In another study, Bielak and colleagues (2007) reported that the associations between activity engagement and 6-year changes in perceptual speed are higher for those over 75 than for those under 75 years. Taken together, these data suggest activity engagement may be especially beneficial for the oldest-old in the memory and attention/perceptual speed domains, potentially because the cognitive or social demands of the activity shift with increasing age (Bielak, 2010). We sought to expand upon these findings in a novel prospective cohort with an older age range that was well-powered for examining risk factors for later-life cognitive decline (Snitz, O'Meara, et al., 2009).

5.2 Activity Subtypes Differentially Predict Specific Cognitive Domains

One contributor to the mixed evidence for a prospective relationship between activity engagement and cognitive change may be the variability in the cognitive tests and activities that are measured (Bielak, 2017). Many studies include a limited set of cognitive tests that include only specific subdomains (e.g., verbal, visuospatial) or response modalities (e.g., oral, written). Failure to evaluate a range of domains and modalities could lead to a lack of precision in

estimation of the association between activity engagement and later-life cognition or the incorrect conclusion that there is no association at all (Small et al., 2013).

Variation in activity measures is also important to consider, because research suggests that different types of activities place different levels of physical, cognitive, and social demands on individuals that may differentially impact their cognition. For example, the exercise literature suggests that highly aerobic activities may be especially protective against memory and executive functioning decline (Erickson et al., 2011; Kramer & Colcombe, 2018; Prakash et al., 2015). Studies including self-reported activity inventories typically find that leisure social and intellectual activities are associated with primarily memory, attention, and perceptual speed (Bielak, 2010; Verghese et al., 2003; Wilson et al., 2002), presumably because this domain declines gradually throughout the lifespan and is sensitive to environmental enrichment (Ghisletta et al., 2006).

Further, lack of knowledge regarding how people with different levels of lifestyle engagement vary *qualitatively* in the types of activities they report prevents further opportunities for intervention. Knowing whether there are distinct groups of individuals that endorse specific types of activities may provide attentional contextual detail, above and beyond just the number of endorsed activities, that could inform where and how to intervene. Information regarding the settings and types of activities that interest people may suggest different motivations for being active within different groups of older adults. Such information has been leveraged previously in other successful nonpharmacological interventions to promote healthy aging (e.g., generativity in the Baltimore Experience Corps sample; Fried et al., 2004).

We implemented the latent class approach introduced in Aim 1 to characterize lifestyle engagement groups which leveraged both amount and types of activities (Collins & Lanza,

2010). Importantly, by grouping individuals by their types of activities, LCA may better characterize lifestyle engagement groups by specifying which types of activities are reported by individuals who have different levels of lifestyle engagement. We previously reported that those with a higher quantity of activity were also more likely to endorse more intellectual activities than those with lower lifestyle engagement (Chapter 4).

Current Study

The purpose of this study was to examine whether groups defined by lifestyle engagement differentially predict global and domain-specific cognitive level and change after adjusting for relevant confounders. Confounders are variables hypothesized to be related to both activity engagement and cognition. They included age (Buchman et al., 2014; Verbrugge et al., 1996), sex (Azevedo et al., 2007; Wu et al., 2017), race (Zahodne et al., 2017), education (Chan et al., 2018; King et al., 2000; Wilson et al., 1999), medical comorbidities (Saunders et al., 2016; Snyder et al., 2015), and depressive symptoms (Glass et al., 2006; Griffiths et al., 1987).

A key goal of this work is to leverage LCA, a data-driven approach, to understand the domain-specific cognitive changes by which differences in activity patterns may protect against the clinical impairments observed in Aim 1. We hypothesized that higher lifestyle engagement, characterized by broader engagement in intellectual activities, is associated with reduced global cognitive declines over time. We further hypothesized that these associations pertain specifically within the memory and attention/perceptual speed domains. We examined this using an extensive neuropsychological battery including tests spanning multiple cognitive domains, subdomains, and response modalities. Better understanding how cognitive trajectories differ across qualitatively-different groups may inform where and for whom researchers should deploy future nonpharmacological interventions.

5.3 Methods

Participants

As in Aim 1, participants were volunteers from the Ginkgo Evaluation of Memory (GEM) study, a randomized clinical trial testing the efficacy of *Ginkgo biloba* supplements for preventing all-cause dementia (DeKosky et al., 2006; Fitzpatrick et al., 2006). Recruitment and eligibility criteria have been covered previously (Chapter 3.1). Briefly, participants were community-dwelling older adults from four study sites: Hagerstown, Maryland (Johns Hopkins University); Pittsburgh, Pennsylvania (University of Pittsburgh); Winston-Salem and Greensboro, North Carolina (Wake Forest University), and Sacramento, California (University of California –Davis). Eligibility criteria included: being free of prevalent dementia and other neurocognitive diseases (e.g., Parkinson's) at baseline, not currently taking certain medications (e.g., warfarin, cholinesterase inhibitors), and identifying a proxy willing to be interviewed at each 6-month visit (DeKosky et al., 2006). Data collection began in September 2000 and ended April 2008.

Measures

Before randomization into the intervention or control group, eligible participants completed an extensive survey battery and functional assessment at baseline measuring their demographic and health characteristics.

Lifestyle Activity Questionnaire (LAQ). The selection of measured activities and operationalization into variety and latent class indicators was identical to the first manuscript (Chapter 4.4). Briefly, participants were asked the frequency with which they participated in 26 everyday activities (e.g., cooking, reading, gardening, etc.) over the past year on a 6-point Likert scale (0 = never/less than once a month, 5 = every day). Items were re-coded as a binary (yes/no)

variable indicating whether participants ever engaged in each activity during the past year. We used a latent class analysis (LCA) approach to group individuals by both quantity and type of activity engagement (Chapter 4.4).

Cognitive functioning. Several standardized neuropsychological measures were administered as part of the GEM Study Neuropsychological Test Battery (NTB; Table 3.1). Memory tests included the California Verbal Learning Test (CVLT) immediate and delayed recall (Delis et al., 1987) and Modified Rey-Osterrieth Complex Figure delayed recall tasks (Becker et al., 1987; Osterrieth, 1944). Tests of visuospatial construction included the Wechsler Adult Intelligence Scale – Revised (WAIS-R) Block Design (Wechsler, 1981) and Modified Rey-Osterrieth Complex Figure copy task. Language tests included the Boston Naming Test (Judith Saxton et al., 2000) and semantic Controlled Oral Word Association Test (COWAT, i.e., animal naming; Spreen & Strauss, 1998). Attention/psychomotor speed tests included the Trail Making Test Part A (TMT-A; Reitan, 1958) and WAIS-R Digit Span Forwards (Wechsler, 1981). Finally, tests of executive functioning included the Stroop Color-Word Test (Trenerry et al., 1989), WAIS-R Digit Span Backwards, and Trail Making Test Part B (TMT-B, adjusted for TMT-A).

All scores on the cognitive tests were standardized based on the mean and standard deviation at baseline. Domain-specific scores (i.e., memory, attention, etc.) were then derived by taking the average of the z-scores on the tests within the domain. For executive functioning, task-switching ability was isolated by first regressing TMT-B on TMT-A to derive an adjusted TMT-B score. Similarly, inhibitory ability (i.e., the Stroop effect) was captured by regressing the Stroop color ink-naming score on the word naming score to produce an adjusted ink-naming score. Histograms by study visit were used to explore distributions of cognitive scores, and

TMT-A and TMT-B scores were log-transformed to correct for negative skew. A global cognition score was derived by averaging across domain-specific z-scores.

Prevalent Mild Cognitive Impairment was also measured in GEM using normative cutoffs on the neuropsychological battery (Snitz, Saxton, et al., 2009). Yet, it was not adjusted for in longitudinal models due to concerns that it may induce collider bias and result in residual confounding with cognitive change over time (Glymour et al., 2005). We did evaluate effect modification by excluding those with MCI in sensitivity analyses.

Descriptive Covariates. Several measures were used to explore demographic and health differences between the activity classes.

Demographics. Baseline demographic variables included age (years), race (white/non-white), education (years), and indicators for study site (Hagerstown, Pittsburgh, Sacramento, Winston-Salem/Greensboro).

Medical Comorbidities. Participants reported their current medical comorbidities and risk factors. These included self-reported hypertension, current/former smoking, diabetes, acute myocardial infarction, heart failure, atrial fibrillation, stroke, and transient ischemic attack. A sum count of each binary (yes/no) response to these variables was generated to measure medical comorbidities.

***Depressive symptoms*.** A modified 10-item Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) was used to measure depressive symptoms (Appendix 2). Items were measured on a 4-point Likert scale (0 = rarely/none of the time, 3 = most of the time). Responses were summed to produce a composite depressive symptom score, and scores ≥10 were identified as potential clinical depression (Björgvinsson et al., 2013). For participants where at least one item was refused or missing, prorating was implemented wherein

missing/refused items were replaced with the mean score among the completed items before computing the final score (Downey & King, 1998). Imputation was only used for the 2.0% (n=60) of participants with missing item-level CES-D responses.

Analytic Strategy

Tabulations and summary statistics (e.g., mean, standard deviations) were generated to compare covariates across activity classes. Spaghetti plots stratified by class were used to examine trends and variance in cognitive performance trajectories over time. Activity class indicators were identical to those derived from Analytical Steps 1 and 2 in the first manuscript (Chapter 4.4). The final analytic sample consisted of 3,068 individuals who had at least one NTB. Participants were followed up for up to 7.5 years (M=5.0, SD=2.4).

Cognitive performance analyses. Linear mixed effects models with random intercepts and slopes were used to model cognitive performance over time (Laird & Ware, 1982). Two advantages of mixed effects modeling are that they use all available observed data and can produce valid estimates under the assumption that data are missing at random, conditional on variables in the model (i.e., MAR; Hogan et al., 2004). Variances were estimated using restricted maximum likelihood estimation (REML) to account for the inclusion of numerous fixed effects (Kenward & Roger, 1997). Time was included as years from study entry to current visit date.

Fixed mean baseline differences and change from baseline across classes were modeled by including class indicators and class by time interactions, respectively. All covariates were measured at baseline and thus included as time-invariant, fixed effects. We estimated a series of nested models. Model 1 included only activity class indicators, time (years), and class by time interactions. Model 2 was adjusted for demographic and health variables, including treatment group (intervention vs. control), indicators for study site, age, sex, race, education (i.e., high

school or less, some college, college graduate, professional/graduate), depression (CES-D≥10), medical comorbidities, and baseline MCI status. Model 2 was also adjusted for interactions of age by time, sex by time, and study site by time. We did this because these were hypothesized to be strong demographic predictors of cognitive functioning over time.

Sensitivity analyses. To account for potential nonlinear changes in cognitive domain scores over time and across baseline age, sensitivity analyses were performed including spline terms: 1) at study year 3 and 2) for five-year intervals of baseline age (i.e., >80, >85, >90). Model fits were evaluated using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), where lower values indicated better fit (Burnham & Anderson, 2004). The additional model fit provided by the spline terms was evaluated using likelihood ratio tests of nested models, where significant tests indicated that the model with additional spline terms fit better than the original model (Glover & Dixon, 2004).

5.4 Results

Sample Characteristics

Descriptive statistics for the current analytic sample (n=3,068) are presented in Table 5.1. The sample had an average age of 78.5 years (SD=3.3, range: 72-96), and was mostly white (95%) and male (54%). Most participants were highly educated, with only 36% having a high school degree or less. About half of participants rated their health as “very good” or “excellent,” few had significant depressive symptoms (7%), and most had few medical comorbidities (Median=1, IQR: 1-2). Most participants were assigned to the Social group (Class 3; n=1,036, 32%), followed by the Least Active (Class 4; n=856, 28%), Social Intellectual (Class 1; n=662, 22%), and Intellectual groups (Class 2; n=514, 18%).

Class Enumeration and Structure

Table 4.3 from Aim 1 of this dissertation presents the class enumeration results (step 1) for 2- through 6-class models. A 4-class model was chosen based on the criteria mentioned previously (Chapter 4.4), although supplemental analyses for a more parsimonious 3-class model were also conducted. Figure 4.1 from Aim 1 is a plot of the item-response probabilities of activity engagement by latent class for the 4-class model. Importantly, there were not only differences in amount of engagement by class, but also differences in types of activities reported across classes. Class 1 (Social Intellectual) had high probabilities of engagement broadly across intellectual and social activities. Class 2 (Intellectual) was likely to engage in specific intellectual (e.g., viewing art, computer use) and some social activities (e.g., movies), but less so in social institutional activities (e.g., volunteering, social clubs, church). In contrast, Class 3 (Social) had high probabilities of engagement in social institutional activities, but was less likely to report intellectual activities. Finally, Class 4 (Least Active) had lower probabilities of engagement in most intellectual and social activities compared to the other classes. Yet, their probabilities of engagement in some home-based activities, such as doing crossword puzzles or playing cards, were comparable to Class 3, suggesting that the main difference between these two classes may be their engagement in social institutional activities.

Supplemental 3-class structure. The 3-class model (Aim 1, Figure 4.2) was highly similar in structure to Classes 1 (Social Intellectual), 3 (Social), and 4 (Least Active) in the 4-class model. The primary difference between the 3- and 4-class models was the addition of Class 2 (Intellectual), which primarily split off from Class 1 (Social Intellectual). Comparing Class 1 in both models, the addition of Class 2 led to slight increases in item-response probabilities for social institutional activities (e.g., volunteering, church) in Class 1. This further supports the characterization of Class 2 as a less social but intellectually-active group.

Cognitive Performance Analyses

Tables 5.2 and 5.3 present unadjusted and adjusted linear mixed effects models for activity classes on global (Table 5.2) and domain-specific (Table 5.3) cognitive performance.

Activity class predicting global cognition. Compared to the Social Intellectual group (Class 1), baseline global cognitive performance was 0.39 SD lower (*SE*=.049, *p*<.001) for the Social group (Class 3) and 0.47 SD lower (*SE*=.051, *p*<.001) for the Least Active group (Class 4) in the unadjusted model (Table 2, Model 1). These baseline differences were attenuated but remained significant in the adjusted model (Social: *B*=-.210, *SE*=.044, *p*<.001; Least Active: -.281, *SE*=.046, *p*<.001). There were no significant differences in baseline global cognitive performance comparing the Intellectual group (Class 2) to the Social Intellectual group (Class 1).

Compared to the Social Intellectual group (Class 1), the Intellectual group (Class 2) had a .017 SD greater annual decline (*SE*=.008, *p*=.045) and the Least Active group (Class 4) had a .025 SD greater annual decline (*SE*=.008, *p*=.001) in the unadjusted model. In the adjusted model, only the longitudinal difference for the Least Active group remained significant (*B*=-.019, *SE*=.008, *p*=.012).

Activity class predicting domain-specific cognition.

Memory. Compared to the Social Intellectual group (Class 1), baseline memory performance was 0.28 SD lower (*SE*=.049, *p*<.001) for the Social group (Class 3) and 0.39 SD lower (*SE*=.051, *p*<.001) for the Least Active group (Class 4) in the unadjusted model (Table 2, Model 1). These baseline differences were attenuated but remained significant in the adjusted model (Social: *B*=-.146, *SE*=.047, *p*=.002; Least Active: -.252, *SE*=.049, *p*<.001).

Compared to the Social Intellectual group (Class 1), the Least Active group (Class 4) had a .026 SD greater annual decline (*SE*=.010, *p*=.007) in the unadjusted model. This longitudinal

difference remained significant in the adjusted model (*B*=-.020, *SE*=.009, *p*=.035). There were no significant differences in baseline or annual change in memory comparing the Intellectual group (Class 2) to the Social Intellectual group (Class 1).

Executive functioning. Compared to the Social Intellectual group (Class 1), baseline executive functioning was 0.34 SD lower (*SE*=.048, *p*<.001) for the Social group (Class 3) and 0.43 SD lower (*SE*=.050, *p*<.001) for the Least Active group (Class 4) in the unadjusted model (Table 2, Model 1). These baseline differences were attenuated but remained significant in the adjusted model (Social: *B*=-.189, *SE*=.047, *p*<.001; Least Active: -.240, *SE*=.050, *p*<.001). There were no significant differences in annual change in executive functioning comparing each group to the Social Intellectual group (*p's*>.05).

Attention. Compared to the Social Intellectual group (Class 1), baseline attention was 0.21 SD lower (*SE*=.048, *p*<.001) for the Social group (Class 3) and 0.28 SD lower (*SE*=.050, *p*<.001) for the Least Active group (Class 4) in the unadjusted model (Table 2, Model 1). These baseline differences were attenuated but remained significant in the adjusted model (Social: *B*=-.093, *SE*=.047, *p*=.049; Least Active: -.143, *SE*=.050, *p*=.004).

Compared to the Social Intellectual group (Class 1), the Least Active group (Class 4) had a .022 SD greater annual decline (*SE*=.008, *p*=.008) in the unadjusted model. This longitudinal difference remained significant in the adjusted model (*B*=-.019, *SE*=.008, *p*=.023). There were no significant differences in annual change in attention comparing the Intellectual (Class 2) or Social group (Class 3) to the Social Intellectual group (Class 1).

Language. Compared to the Social Intellectual group (Class 1), baseline language was 0.32 SD lower (*SE*=.048, *p*<.001) for the Social group (Class 3) and 0.30 SD lower (*SE*=.050, *p*<.001) for the Least Active group (Class 4) in the unadjusted model (Table 2, Model 1). These

baseline differences were attenuated but remained significant in the adjusted model (Social: *B*=-.186, *SE*=.045, *p*<.001; Least Active: -.174, *SE*=.048, *p*<.001). There were no significant differences in annual change in language comparing each group to the Social Intellectual group (*p's*>.05).

Visuospatial construction. Compared to the Social Intellectual group (Class 1), baseline visuospatial construction performance was 0.23 SD lower (*SE*=.050, *p*<.001) for the Social group (Class 3) and 0.23 SD lower (*SE*=.052, *p*<.001) for the Least Active group (Class 4) in the unadjusted model (Table 2, Model 1). These baseline differences were attenuated but remained significant in the adjusted model (Social: *B*=-.110, *SE*=.044, *p*=.012; Least Active: -.152, *SE*=.046, *p*=.001). There were no significant differences in baseline global cognitive performance comparing the Intellectual group (Class 2) to the Social Intellectual group (Class 1).

Compared to the Social Intellectual group (Class 1), the Intellectual group (Class 2) had a .034 SD greater annual decline (*SE*=.009, *p*<.001) and the Least Active group (Class 4) had a .024 SD greater annual decline (*SE*=.008, *p*=.004) in the unadjusted model. In the adjusted model, only the longitudinal difference for the Intellectual group remained significant (*B*=-.021, *SE*=.009, *p*=.021).

Sensitivity analyses.

Results and fit statistics from sensitivity analyses including spline terms to account for potential nonlinear relationships are included in Supplemental Tables 5.1-5.6. Including a spline term at year 3 resulted in better fit compared to the models including continuous time (i.e., years from study baseline) only (*p*'s<.001 for likelihood ratio tests comparing original and Year 3 spline models). Including spline terms for baseline age did not consistently improve model fit across cognitive domains.

Early versus later longitudinal differences. Overall, the Year 3 spline models suggested that the differences in annual change observed in the original models occurred primarily after 3 years in the study. For memory (Supplemental Table 5.2, Model D), the difference in change between the Social Intellectual and Least Active groups changed from .007 SD per year before year 3 (*SE*=.017, *p*=.690) to -.045 SD after year 3 (*SE*=.017, *p*=.010). The difference in change between the Social Intellectual and Least Active groups for attention was no longer significant in the spline model (*p*'s>.05; Supplemental Table 5.5, Model B). The difference in change between Social Intellectual and the Intellectual groups for visuospatial construction was also attenuated past statistical significance, but there was still a trending relationship for change past year 3 (*B*=-.034, *SE*=.019, *p*=.076), suggesting that this difference may be related to loss of statistical power and increased variance from estimating additional spline terms.

Effect modification by MCI. We found a similar pattern of results for most domains after excluding those individuals with prevalent MCI (Supplemental Table 5.7). For visuospatial construction, we no longer observed baseline differences (*p*'s>.05) compared to the Social Intellectual group. Yet, there were significant longitudinal differences between Intellectual (*B*=-.022, *SE*=.009, *p*=.015) and Least Active (*B*=-.021, *SE*=.008, *p*=.014) groups compared to the Social Intellectual group. This suggests that the baseline differences in visuospatial construction observed in the overall sample (Table 5.3) were likely driven by prevalent MCI cases, but the Social Intellectual group still had reduced annual declines even after limiting the sample to individuals without MCI.

5.5 Discussion

To our knowledge, this study is among the first to examine how lifestyle engagement groups that differed in amount and types of self-reported activities also differed in domain-

specific cognitive trajectories. We found that the Social Intellectual group had better baseline global cognition, as well as better baseline performance across every domain compared to the Social and Least Active groups. The Social Intellectual group also had reduced declines in global cognition, memory, and visuospatial construction compared to the Least Active group. These associations remained significant after adjusting for several relevant confounders. These findings are consistent with prior work suggesting that higher activity variety, especially for intellectual activities, may attenuate aging-related cognitive declines (Bielak et al., 2007; Carlson et al., 2012; Hultsch et al., 1999).

Several potential mechanisms may explain the relationship between lifestyle engagement and cognitive decline. Engagement in a higher variety of activities may buffer against cognitive declines through requiring individuals to navigate a complex environment, leading to greater utilization and maintenance of cognitive abilities (Schooler, 1984). Similarly, the enrichment hypothesis (Hertzog et al., 2009) posits that engagement in diverse activities may moderate neurocognitive impairments through maintenance or enhancement of cognitive abilities or through provision of compensatory mechanisms. Higher activity variety may also buffer against accumulated pathologies through structural (e.g., grey matter volume) and functional (e.g., functional connectivity) brain changes (Stern, 2002).

The current results suggest that promoting high lifestyle engagement in later life may be key to preventing loss of memory abilities necessary for maintaining daily functioning and well-being. We found the largest longitudinal differences between the Social Intellectual and Least Active groups for memory performance. These findings expand upon Aim 1 of this dissertation by suggesting that higher later-life lifestyle engagement may protect against clinical impairments by preserving memory performance. Memory declines are the hallmark behavioral marker of

Alzheimer's Disease, the most prevalent form of dementia (American Psychiatric Association, 2013). Memory declines also contribute significantly to difficulties completing activities of daily living in older adulthood (Farias et al., 2009).

There were no baseline differences between Social Intellectual and Intellectual groups, but the Intellectual group had a higher annual decrease in visuospatial construction over time. These groups were primarily distinguished by their level of social institutional engagement. Higher community engagement within the Social Intellectual group may place increased demands on visuospatial skills by requiring older adults to navigate a complex environment (Carlson & Varma, 2015; Schooler, 1984). Given that these groups began at the same baseline level of visuospatial construction, the additional cognitive enrichment offered by social institutional engagement may be important to preserving visuospatial skills throughout later life.

We also found differences between the Social Intellectual and Least Active groups in baseline performance across all domains, but particularly for memory, attention, and executive functioning. Yet, there were not consistent group differences in trajectories of attention and executive functioning over time. Some studies have also reported that aging-related declines in attention and executive functioning abilities may precede declines in global cognition and memory (Carlson et al., 2009; Clark et al., 2012). It is therefore unsurprising that lifestyle engagement measured in later life may be a proxy for existing baseline reserves in these domains. Yet, other studies have found that episodic memory declines before executive functioning, especially in clinical samples (Albert et al., 2007; Saxton et al., 2004).

Interpreting the current findings within the existing literature, lifestyle engagement at certain points in the lifespan may be most protective for the specific cognitive abilities that are most sensitive to normative changes during that life stage (Bielak et al., 2014). Later life (i.e.,

>70 years) may be an important period to remain active to protect against future memory declines. While it is important to acknowledge potential survivorship bias (i.e., healthy survivor effect) with all older-aged samples (Hernán et al., 2004), this finding is still important given recent increases in active life-expectancy post-retirement (Crimmins et al., 2016). With older adults living longer, there are opportunities for new or renewed activity engagement that could be leveraged to benefit their future memory performance.

One advantage of the current LCA approach is that we did not rely on *a priori* specification of activity domains or aggregate all activities into a single variety metric. This was especially important for revealing the qualitative difference in social engagement between the groups, where the Social Intellectual group (Class 1) had a high likelihood of participating in most social activities, but those in the Social group (Class 3) had a high likelihood of engaging in only social institutional activities (e.g., church). This splitting of social activities into leisure and institutional subdomains is not typically done in research using activity frequency, or variety measures (Bielak, 2017; Hultsch et al., 1999b; Parisi et al., 2012).

Despite having high institutional social engagement, we found that the Social group had poorer baseline global and domain-specific cognitive performance than the Social Intellectual and Intellectual groups. This may be due to differences in socioeconomic status (SES) between the two groups, as the Social Intellectual and Intellectual groups were more likely to endorse going to movies, concerts, or plays. The Social Intellectual and Intellectual groups were also more likely to be higher educated (Aim 1, Table 4.2). Individuals with higher SES may have enhanced brain reserve (Stern, 2002), expanded social networks (Fratiglioni et al., 2004), expanded life space (James, Boyle, Buchman, Barnes, et al., 2011), increased physical activity (Najar et al., 2019; Ströhle et al., 2015; Voss et al., 2014), or additional cognitive stimulation

related to novel environmental experiences (e.g., attending new concerts more frequently). Unfortunately, additional SES measures (e.g., wealth, income) were unavailable in the current dataset, but other studies have found an independent relationship between activity engagement and cognitive outcomes after adjusting for these measures (Bennett et al., 2014; Wilson et al., 2007).

Alternatively, the Social Intellectual and Intellectual groups also had maintained engagement in intellectual activities in later life (e.g., taking courses), and intellectual engagement in particular has been found to be especially predictive of cognitive functioning (Bielak, 2010; Hultsch et al., 1999b). Interestingly, there were no differences in annual rate of change in cognitive performance between the Social Intellectual and Social groups in any domain. This suggests that the social connections and engagement in the Social group may provide some protection against future cognitive declines, despite this class starting at a lower baseline level of cognition than the Social Intellectual group.

Ultimately, the lifestyle engagement groups presented here may be useful for planning future interventions. While differences in number of activities may be important for determining an individual's activity variety (Carlson et al., 2012), further information on qualitative differences in types of engagement may help pinpoint novel settings and behaviors to target. The Intellectual group (Class 2), for example, may be more motivated to participate in a cognitively-intensive intervention, such as the Senior Odyssey, where participants work together to solve complex problems involving critical thinking and creativity (Parisi et al., 2007). In contrast, the Social group (Class 3) may be more motivated to participate in an intervention tied to social engagement or nested within a social institution, such as their church or social club. Given that they had worse memory trajectories, those the Social group may also benefit from an

intervention focused on improving memory (e.g., memory training; Gross et al., 2012). Integrating new interventions into existing activity contexts may ultimately promote more sustainable behavioral changes relevant to prevention of cognitive declines, by directly linking the intervention with engagement that already gives individuals purpose in life (Boyle et al., 2010).

There are limitations to the current study. As reported in Aim 1 (Chapter 4.6), we used a retrospective, self-reported inventory to measure activity engagement, which may result in recall bias. We attempted to mitigate recall bias by only using dichotomous (yes/no) activity responses that did not require recall of precise frequencies of engagement. Second, our sample was mostly white participants in a clinical trial, and the current findings warrant further replication and measurement invariance testing in more diverse samples.

The current study also had several strengths. We used a well-characterized sample of adults at higher age-related risk of cognitive declines. Our sample was well-powered to detect differences in both baseline and longitudinal cognitive performance (Snitz, O'Meara, et al., 2009). We also measured each cognitive domain using at least two tests that spanned different subdomains and response modalities, ideally providing more precise estimates of these cognitive domains. Finally, our novel application of a person-centered LCA approach demonstrated that individuals group naturally by both amount and types of activities, and revealed qualitative differences in engagement that could imply potential motivational differences for staying active in later life. Our study is the first, to our knowledge, to show that these lifestyle engagement groups also differed in global and domain-specific cognitive trajectories over time.

5.6 Conclusion

Increasing active life expectancies after retirement provide novel opportunities for encouraging lifestyle engagement in later life. The question remains as to how to quantify lifestyle engagement in a way that is useful both for predicting relevant health outcomes and for deploying health-related interventions. The current findings suggest that individuals group naturally by both quantitative and qualitative differences in activity engagement, where those with the highest lifestyle engagement also engage broadly in intellectual and social activities. Building upon Aim 1 of this dissertation, the current findings suggest that high lifestyle engagement may protect against clinical neurocognitive impairments by providing greater baseline global cognitive resources while also mitigating against declines in specific domains (e.g., memory, visuospatial construction) highly related to independent functioning in later life.

Chapter 6: Higher Lifestyle Engagement Predicts Reduced Risk of Prevalent Frailty Criteria but Not Attenuated Risk over Time (Aim 3)

Older adults often experience reduced physical activity in later life (Varma et al., 2014), which can contribute to incident mobility declines (Rosso, Studenski, et al., 2013) and physical frailty (Fried, Tangen, et al., 2001). Nevertheless, later life also provides an opportunity for continued engagement in fulfilling activities that encourage daily physical exercise. Activities that are cognitively- (e.g., taking courses) and socially-enriching (e.g., attending church) may provide additional purpose in life (Boyle et al., 2010) that could contribute to sustained engagement over time. Better understanding how individuals group together based on their self-reported lifestyle activities, here termed "lifestyle engagement groups," may provide insight into motivational and contextual factors that may be relevant to designing future, sustainable interventions. Furthermore, it is currently unknown whether such lifestyle engagement groups, characterized by differences in social or cognitive engagement, may differ in existing or future risk of physical impairments. The current work expands upon the first two aims of this dissertation by examining whether the protective association of lifestyle engagement extends to physical outcomes, including mobility and physical frailty criteria.

6.1 Physical Frailty and Mobility: Connections with Lifestyle Engagement

Physical frailty is a clinical state of increased vulnerability to adverse health outcomes (e.g., disability, falls, mortality). The physical frailty phenotype consists of five criteria: 1) unintentional weight loss, 2) low strength, 3) exhaustion, 4) slow walking, and 5) low physical activity (Fried, Tangen, et al., 2001). Physical frailty is not uncommon, and it is estimated that 15% of community-dwelling older adults in the United States are frail (≥3 criteria) while 45% are prefrail (1-2 criteria) (Bandeen-Roche et al., 2015). Physical frailty is also strongly associated

with incident disability and injury. Of those in the US considered frail, 42% were hospitalized and about 55% had a fall in the previous year (Bandeen-Roche et al., 2015).

Mobility, the ability of an individual to move about their environment (Rosso, Studenski, et al., 2013), is highly related to both physical frailty (Fried, Tangen, et al., 2001) and lifestyle engagement (Baker et al., 2003). An individual's mobility contributes to their gait speed and physical activity, two criteria of the frailty phenotype. Furthermore, mobility is a key component to an actively-engaged lifestyle in later life, even beyond just physical exercise (Baker et al., 2003). Certain social (e.g., volunteering, social clubs) activities require either sufficient inherent mobility or additional support mechanisms (e.g., assistive devices, transportation assistance) to maintain meaningful engagement (Xue, Fried, et al., 2008).

Physical frailty may also be linked to lifestyle engagement through the body's stress response. Dysregulated energetics from declining physiologic systems are thought to lead to chronic activation of stress systems (Ferrucci & Fabbri, 2018; Xue et al., 2019). Lifestyle engagement may ultimately build physiologic and neural reserves that buffer against stress through increased cognitive engagement (Hertzog et al., 2009; Stern, 2002; Xue et al., 2019).

Given that lifestyle engagement and physical frailty may be linked through mobility or stress pathways, it is plausible that lifestyle engagement may be protective against future frailty through maintenance of physical reserves (Fried, Tangen, et al., 2001; Varma, Hausdorff, et al., 2016; Xue, Fried, et al., 2008; Xue et al., 2019). On the other hand, an individual's lifestyle engagement in later life is likely also limited by their existing frailty criteria. Unsurprisingly, those with more severe life-space constriction (e.g., unable to leave home) have been found to have more prevalent mobility difficulties (e.g., walking ¼ mile; Xue et al., 2008). Dissociating the cross-sectional and longitudinal associations between late-life lifestyle engagement and

physical frailty is therefore an important first step to determining how to intervene on lifestyle to improve physical functioning in later life.

6.2 Lifestyle Engagement as a Potential Protective Factor Against Physical Frailty

Only a few studies have examined the longitudinal relationship between engagement in self-reported cognitively- and socially-demanding lifestyle activities and physical functioning. Buchman et al. (2009) examined whether self-reported social engagement predicted changes in objectively-measured mobility over time in the Rush Memory and Aging Project (MAP). The study used a global mobility composite of 18 measures capturing whole-body motion (e.g., walking speed, finger tapping, elbow flexion). They found that lower frequency of social engagement was associated with larger annual declines in mobility, which were in turn associated with a higher risk of death and disability (Buchman et al., 2009). The association remained significant after adjusting for frequency of cognitive and physical activity, suggesting that social engagement had an independent protective association with mobility functioning in later life.

There have been relatively more studies examining the link between lifestyle engagement and incident self-reported functional disability (Avlund et al., 2004; James, Boyle, Buchman, & Bennett, 2011; Mendes de Leon et al., 2003; Unger et al., 1997). Functional disability includes difficulties completing instrumental activities of daily living (IADLs, e.g., shopping) or activities of daily living (ADLs, e.g., bathing) that are important to maintaining independence and quality of life in older adulthood (Branch et al., 1984). In the New Haven Established Populations for Epidemiologic Studies of the Elderly (EPESE), Mendes de Leon et al. (2003) found that while higher social engagement was associated with reduced disability at baseline, this protective association diminished over time. In contrast, others have found that more frequent social

engagement was associated with reduced incidence of first-time ADL, IADL, and mobility difficulties (Avlund et al., 2004; James, Boyle, Buchman, & Bennett, 2011) and buffered against declines in these abilities over time (Unger et al., 1997).

Current Study

Given that physical frailty may manifest after initial declines in global mobility but before incident disability with IADLs and ADLs (Xue, Bandeen-Roche, et al., 2008), we hypothesized that higher lifestyle engagement in our study would be associated with lower risk of prevalent frailty criteria, especially mobility limitations (i.e., slow gait), and potentially reduced risk of incident frailty criteria over time. We examined this relationship using a novel application of latent class analysis to characterize lifestyle engagement (Chapter 4.4) that groups individuals based on their self-reported variety of social, intellectual, and physical activities. This approach further expands on the current literature by investigating whether differences in variety of activities (Carlson et al., 2012), rather than frequency, may protect against incident physical frailty criteria.

Finally, we adjusted models for relevant covariates to isolate the independent associations between lifestyle engagement and physical frailty criteria. These covariates included age (Bandeen-Roche et al., 2015; Buchman et al., 2014), sex (Azevedo et al., 2007; Fried, Tangen, et al., 2001), race (Bandeen-Roche et al., 2015; Chan et al., 2018), education (Bandeen-Roche et al., 2015; King et al., 2000), number of medical comorbidities (Fried, Tangen, et al., 2001; Saunders et al., 2016), and depressive symptoms (Glass et al., 2006; Griffiths et al., 1987).

6.3 Methods

Participants

As in Aims 1 and 2, participants were volunteers from the Ginkgo Evaluation of Memory (GEM) study, a randomized clinical trial testing the efficacy of *Ginkgo biloba* supplements for preventing all-cause dementia (DeKosky et al., 2006; Fitzpatrick et al., 2006). Briefly, participants were community-dwelling older adults from four study sites: Hagerstown, Maryland (Johns Hopkins University); Pittsburgh, Pennsylvania (University of Pittsburgh); Winston-Salem and Greensboro, North Carolina (Wake Forest University), and Sacramento, California (University of California –Davis). Eligibility criteria included: being free of prevalent dementia and other neurocognitive diseases (e.g., Parkinson's) at baseline, not currently taking certain medications (e.g., warfarin, cholinesterase inhibitors), and identifying a proxy willing to be interviewed at each 6-month visit (DeKosky et al., 2006). Data collection began in September 2000 and ended April 2008.

Measures

Before randomization into the original intervention or control group, eligible participants completed an extensive survey battery and functional assessment at baseline measuring their demographic and health characteristics. Participants also completed vital exhaustion measures every six-months after randomization, as well as a usual walking test during annual visits.

Lifestyle Activity Questionnaire (LAQ). The selection of measured activities and operationalization into latent class indicators was identical to the first manuscript (Chapter 4.4). Briefly, participants were asked the frequency with which they participated in 26 everyday activities (e.g., cooking, reading, gardening, etc.) over the past year on a 6-point Likert scale (0 = never/less than once a month, 5 = every day). Items were re-coded as a binary (yes/no) variable

indicating whether or not participants ever engaged in each activity during the past year. We used a latent class analysis (LCA) approach to group individuals by both quantity and types of activity engagement (Chapter 4.4).

Usual gait speed. Participants were asked to walk for 15 feet on a standardized, straight course at their usual pace. They could use a cane or any necessary walking aids during the task. Their time (sec.) to walk the course was recorded at 3 feet and 15 feet markers. Sex- and height-specific cutoffs were used to identify individuals with slow gait (Fried, Tangen, et al., 2001). Individuals with slow gait included: 1) men with height ≤173 cm and time ≥7 seconds, 2) men with height >173 cm and time ≥6 seconds, 3) women with height ≤159 cm and time ≥7 seconds, 4) women with height >159 cm and time ≥6 seconds.

Exhaustion. Two self-reported measures of perceived physical exhaustion were used in this study. The first was derived from the Fried et al. (2001) frailty criteria for exhaustion using two items from the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). These items included "I felt that everything I did was an effort" and "I could not get going." Individuals who reported experiencing either of these symptoms at least a "moderate amount of time" during the past week were categorized as having exhaustion.

We also derived a second measure of exhaustion using four items from the Maastricht Vital Exhaustion Questionnaire (Appels et al., 1987). Participants were asked whether they recently experienced any of the following: "often feel tired," "ever wake up with a feeling of exhaustion or fatigue," "feel weak all over," and "have the feeling that you could not cope with everyday problems as well as you used to." Participants reporting at least two of the four items were categorized as having exhaustion.

Weakness. Given that there were no objective grip strength measures available in GEM, we adapted a measure of self-reported difficulties with gripping, which had been shown to be a valid proxy for objectively-measured grip strength (Liu et al., submitted). Participants were asked: "Do you have any difficulty gripping with your hands?" Those responding "yes" were categorized as having grip weakness, and prevalence of grip weakness was used as an outcome measure in Aim 3.

The four indicators of physical frailty included above (i.e., slow gait, CES-D exhaustion, Maastricht exhaustion, weakness) were analyzed separately rather than in a composite frailty indicator. This was done both to elucidate potential mechanisms by which lifestyle activity may act on frailty, and to account for the relatively low prevalence of participants meeting the cutoff for frailty (>=3 criteria) at baseline (Liu et al., submitted).

Descriptive Covariates. Several measures were used to explore and adjust for demographic and health differences between the activity classes at baseline.

Demographics. Baseline demographic variables included age (years), race (white/non-white), education (years), GEM treatment group, and study site (Hagerstown, Pittsburgh, Sacramento, Winston-Salem/Greensboro).

Medical Comorbidities. Participants reported their current medical comorbidities and risk factors. These included self-reported hypertension, current/former smoking, diabetes, acute myocardial infarction, heart failure, atrial fibrillation, stroke, and transient ischemic attack. A sum count of each binary (yes/no) response to these variables was generated to measure total medical comorbidities.

Depressive symptoms. A modified 10-item Center for Epidemiologic Studies Depression Scale (CES-D; (Radloff, 1977) was used to measure baseline depressive symptoms (Appendix

2). Items were measured on a 4-point Likert scale (0 = rarely/none of the time, 1 = some/little of the time, 2 = moderate amount of time, 3 = most of the time). Responses were summed to produce a composite depressive symptom score, and scores ≥10 were identified as potential clinical depression (Björgvinsson et al., 2013).

Analytic Strategy

Tabulations and summary statistics (e.g., mean, standard deviations) were generated to compare covariates across activity classes. Spaghetti plots stratified by class were used to examine average trends and variance in gait speed trajectories over time. Lowess plots stratified by class were used to examine average trends in binary outcomes over time. Activity class indicators were identical to those derived from Analytical Steps 1 and 2 in the first manuscript (Chapter 4.4). The final analytic sample consisted of 3,068 individuals who had at least one assessment of each physical outcome. All physical outcomes were assessed for up to 7.5 years after baseline (Gait speed: *M*=4.9, *SD*=2.0; Exhaustion/weakness: *M*=5.5, *SD*=1.8).

Mixed effects logistic regressions with random intercepts and slopes were used to model the physical functioning outcomes over time (Breslow & Clayton, 1993; Pinheiro & Chao, 2006). Three advantages of mixed effects modeling are that it uses all available observed data, better accounts for uneven follow-up time between visits in GEM compared to generalized estimating equations, and provides valid estimates under the assumption that data are missing at random conditional on the variables in the model (i.e., MAR; Breslow & Clayton, 1993). Models were fit using adaptive Gauss-Hermite quadrature (Pinheiro & Chao, 2006). Time was included as years from study entry to current visit date. Fixed effects for mean baseline differences and change from baseline across classes were modeled by including class indicators and class by time interactions, respectively. All covariates were measured at baseline and thus included as

time-invariant, fixed effects. Model 1 included only activity class indicators, time (years), and class by time interactions. Model 2 was adjusted for demographic and health variables, including treatment group (intervention vs. control), study site, age, sex, race, education, depression (CES-D≥10), and number of medical comorbidities. Model 2 was also adjusted for interactions of age by time, sex by time, and study site by time. These variables were hypothesized to be strong demographic predictors of physical functioning over time.

Sensitivity analyses. Exploratory analyses revealed potential nonlinear changes in physical outcomes across classes over time, and thus sensitivity analyses were performed where linear spline terms for each year were included and significant spline terms were preserved. Model fits were then evaluated using the Akaike's Information Criterion and the Bayesian Information Criterion, where lower values indicated better fit (Burnham & Anderson, 2004). Sensitivity of parameter estimates to estimation procedure was also examined by varying the number of integration points (i.e., 7, 15, 30) used to fit the model (Pinheiro & Chao, 2006). Finally, we also conducted a sensitivity analysis adjusting for prevalent MCI as adjudicated using the GEM Neuropsychological Test Battery and CDR scale (Snitz, Saxton, et al., 2009), given that existing cognitive impairments have been associated with higher incidence of physical frailty (Gross et al., 2016; Raji et al., 2010).

6.4 Results

Sample Characteristics

Descriptive statistics for the current analytic sample (n=3,068) are presented in Table 6.1. The sample had an average age of 78.5 (SD=3.3, range: 72-96), and was mostly white (95%) and male (54%). Most participants were highly educated, with only 36% having a high school degree or less. About half of participants rated their health as "very good" or "excellent," few had

significant depressive symptoms (7%), and most had few medical comorbidities (M=1.4, SD=1.1). Participants were approximately evenly distributed across activity classes.

Class Enumeration and Structure

Table 4.3 from Aim 1 of this dissertation presents the class enumeration results (step 1) for 2-, 3-, 4-, and 5-class models. A 4-class model was chosen based on the procedure mentioned previously (Chapter 4.5), although supplemental analyses for a more parsimonious 3-class model were also conducted. Figure 4.1 from Aim 1 is a plot of the item-response probabilities of activity engagement by latent class for the 4-class model. Importantly, there were not only differences in amount of engagement by class, but also differences in types of activities chosen across classes. Class 1 (Social Intellectual) had higher probabilities of engagement in intellectual activities (e.g., viewing art) than Classes 3 (Social) and 4 (Least Active). Class 2 (Intellectual) was likely to engage in specific intellectual (e.g., viewing art, computer use) and some social activities (e.g., movies), but less so in social institutional activities (e.g., volunteering, social clubs, church). Both Class 1 (Social Intellectual) and Class 3 (Social) had high engagement in social institutional activities (e.g., church) compared to Classes 2 (Intellectual) and 4 (Least Active). Finally, Class 4 (Least Active) had lower probabilities of engagement in most intellectual and social activities compared to the other classes. Yet, their probabilities of engagement in some home-based intellectual activities, such as doing crossword puzzles or playing cards, were comparable to Class 3 (Social), suggesting that the main difference between these two classes may be their engagement in social intuitional activities.

Physical Frailty Analyses

Table 6.2 presents the unadjusted and adjusted mixed effects logistic models for activity classes on physical frailty criteria over time. Odds ratios are conditional on the random effects,

and are therefore interpreted as the difference in risk of the symptom for an "average" individual (i.e., random intercept and slope are 0). Figure 6.1 presents the average and subject-specific marginal predicted probabilities for each frailty outcome based on the adjusted models. The predicted probabilities are marginalized according to the subject-level random effects, and the average marginal predicted probabilities represent population-level risk over time.

Activity class predicting slow gait. Compared to those the Social Intellectual group (Class 1), baseline odds of slow gait were 2.91 times higher (*95% CI:*[1.44, 5.90], p=.003) for the Intellectual group (Class 2), 2.72 times higher (*95% CI:*[1.47, 5.04], p=.002) for the Social group (Class 3), and 7.06 times higher (*95% CI:*[3.79, 13.13], p<.001) for the Least Active group (Class 4) in the unadjusted model (Table 2, Model 1). These baseline differences were attenuated but remained significant in the adjusted model (Class 2 vs. 1: *OR*=2.89, *95% CI:*[1.45, 5.74], p=.002; Class 3 vs. 1: *OR*=2.04, *95% CI:*[1.11, 3.74], p=.021; Class 4 vs. 1: *OR*=4.24, *95% CI:*[2.30, 7.81], p<.001).

The odds of slow gait in the Social Intellectual group increased by 74% annually in the unadjusted model (*95% CI:*[1.53, 1.97], p<.001) and 34% annually in the adjusted model (*95% CI:*[1.13, 1.60], p=.001). The Intellectual group (Class 2) had a significant 15% annual reduction in odds ratio compared to the Social Intellectual group (Class 1) (*95% CI:*[0.73, 1.00], p=.048) in the adjusted model only. There were no significant differences in annual change in odds of slow gait between the Social Intellectual group (Class 1) and the Social (Class 3) or Least Active (Class 4) groups (*p's*>.05). After 6.5 years in the study, the average marginal predicted probability for the Least Active group was about 40%, compared to about 27% for the Social Intellectual group (Figure 6.1).

Activity class predicting exhaustion.

CES-D Exhaustion. Compared to the Social Intellectual group (Class 1), baseline odds of CES-D exhaustion were 2.31 times higher (*95% CI:*[1.70, 3.15], $p<.001$) for the Least Active group (Class 4) in the unadjusted model (Table 2, Model 1). This baseline difference remained significant in the adjusted model (Least Active: *OR*=1.85, *95% CI:*[1.38, 2.48], $p<.001$). There were no baseline differences in odds of exhaustion comparing the Social Intellectual group with the Intellectual (Class 2) or Social (Class 3) groups.

The odds of CES-D exhaustion for the Social Intellectual group increased by 17% annually in the unadjusted model (*95% CI:*[1.11, 1.23], $p<.001$) and 13% annually in the adjusted model (*95% CI:*[1.04, 1.21], $p=.002$). The Least Active group (Class 4) had a significant 7% annual reduction in odds ratio compared to the Social Intellectual group in both the unadjusted (*95% CI:*[0.87, .99], $p=.027$) and adjusted models (*95% CI:*[0.87, .99], $p=.035$). There were no significant differences in annual change in odds of CES-D exhaustion between the Social Intellectual group and the Intellectual or Social groups (*p's*>.05). After 6.5 years in the study, the average marginal predicted probability for the Least Active group was about 25%, compared to about 23% for the Social Intellectual group (Figure 6.1).

Maastricht Vital Exhaustion. Compared to the Social Intellectual group (Class 1), baseline odds of Maastricht vital exhaustion were 2.13 times higher (*95% CI:*[1.51, 3.01], $p<.001$) for the Least Active group (Class 4) in the unadjusted model (Table 2, Model 1). This baseline difference remained significant in the adjusted model (Least Active: *OR*=1.69, *95% CI:*[1.21, 2.37], $p=.002$). There were no baseline differences in odds of exhaustion comparing the Social Intellectual group with the Intellectual (Class 2) and Social (Class 3) groups.

The odds of Maastricht vital exhaustion for the Social Intellectual group increased by 22% annually in the unadjusted model (*95% CI:*[1.15, 1.29], $p<.001$) and 14% annually in the

adjusted model (*95% CI:*[1.06, 1.23], $p<.001$). There were no significant differences in annual change in odds ratios of Maastricht vital exhaustion between any of the lifestyle engagement groups (*p's*>.05).

Activity class predicting grip weakness. Compared to the Social Intellectual group (Class 1), there were no significant differences in odds of grip weakness at baseline between groups (*p's*>.05). The odds of grip weakness for the Social Intellectual groupremained stable over time in both unadjusted (*OR*=1.00, *95% CI:*[.91, 1.10], $p=.958$) and adjusted (*OR*=.92, *95% CI:*[.80, 1.05], $p=.215$) models, and there were no significant differences over time between groups (*p's*>.05).

Sensitivity analyses. Estimates from sensitivity analyses using the 3-class model are included in Supplemental Table 6.1. Overall, there were few differences between the 4- and 3-class estimates. Notably, there was a significant increase in risk of grip weakness over time for the Social group (Class 2) compared to the Social Intellectual group (Class 1; *OR*=1.13, *95% CI*: [1.02, 1.26], $p=.023$) in the 3-class model that was not maintained when including the 4-class indicators.

In general, including a spline terms for time resulted in comparable or worse AIC and BIC compared to the models including continuous time (i.e., years from study baseline) only. Estimates also did not change substantially when varying the number of integration points.

Prevalent MCI was associated with increased baseline odds of slow gait (*OR*=2.84, *95% CI*: [1.93, 4.18], $p<.001$; Supplemental Table 6.2) and exhaustion (CES-D: *OR*=1.74, *95% CI*: [1.38, 2.18], $p<.001$, Maastricht: *OR*=1.62, *95% CI*: [1.24, 2.12], $p<.001$), but not weakness (*OR*=1.05, *95% CI*: [0.77, 1.43], $p=.755$). Further adjusting for prevalent MCI did not substantially change the baseline estimates of class differences from the original models

(Supplemental Table 6.2, Model 1). The interaction between prevalent MCI and time was only significant for the model of CES-D exhaustion (*OR*=0.93, *95% CI*: [0.87, 1.00], *p*=.041, Supplemental Table 6.2, Model 2), and including this term slightly attenuated the longitudinal difference in odds of exhaustion between the Social Intellectual and Least Active groups (*OR*=0.94, *95% CI*: [0.88, 1.00], *p*=.058).

6.5 Discussion

To our knowledge, this study is the first to examine how individuals who grouped by patterns of social and cognitive lifestyle activities also differed in risk of physical frailty criteria. We found that those highly engaged in *both* intellectual and social activities had lowest risk of slow gait and exhaustion at baseline compared to the less active groups. These associations remained significant after adjusting for several relevant confounders. Yet, there were few differences between lifestyle engagement groups in changes in risk over time. These findings agree with prior research suggesting that a high lifestyle engagement, characterized by a variety of intellectual and social activities in later life, is highly related to existing physical functioning but may not necessarily modify the trajectory of future declines (Mendes de Leon et al., 2003).

Several potential mechanisms may explain the relationship between lifestyle engagement and physical frailty. Mobility is highly related to both the frailty phenotype (Fried, Tangen, et al., 2001) as well as maintaining an active lifestyle (Baker et al., 2003). Certain social (e.g., volunteering, social clubs) activities require either sufficient inherent mobility (e.g., life-space; Xue, Fried, et al., 2008) or additional support mechanisms (e.g., assistive devices, transportation assistance) to maintain meaningful engagement. Physical frailty may also be linked to lifestyle engagement through the body's stress response. Dysregulated energetics from declining physiologic systems are thought to lead to chronic activation of stress systems, including the

innate immune system, hypothalamic-pituitary-adrenal (HPA) axis, and the sympathetic nervous system (Ferrucci & Fabbri, 2018; Xue et al., 2019). These systems are also implicated in aging-related cognitive declines (Franceschi et al., 2006; Robertson et al., 2013). Lifestyle engagement may ultimately be associated with physiologic and neural reserves that buffer against stress through increased cognitive engagement (Hertzog et al., 2009; Stern, 2002; Xue et al., 2019).

Examining the frailty criteria separately enabled us to pinpoint which mechanistic pathways within the frailty cycle are likely the most related to maintaining a complex, active lifestyle in older adulthood. Baseline probabilities of slow gait appeared to follow an approximate dose-response relationship with degree of lifestyle engagement. The highly active Social Intellectual group had the lowest risk of slow gait at baseline, followed by the Intellectual and Social groups, who had relatively similar odds. Furthermore, compared to the Least Active group, the Social Intellectual group had less risk of self-reported exhaustion at baseline on both the CES-D and Maastricht Questionnaire measures. In contrast, there were no differences between groups in self-reported grip weakness. Together, these findings suggest that lifestyle engagement, as measured by the current activities, may primarily be related to existing physiologic reserves through demands on lower-extremity mobility, rather than upper-extremity strength. This agrees with other research that has found large baseline associations between social activity engagement and both global mobility (Buchman et al., 2009) and disability measures (Avlund et al., 2004; James, Boyle, Buchman, & Bennett, 2011; Mendes de Leon et al., 2003) that capture lower-extremity functioning.

This finding is ultimately important, because it suggests that lifestyle engagement may be modifiable in the face of declines in strength. Although physical frailty may manifest from insults at any stage of the cycle, declines in muscle strength often begin in midlife and presage

other frailty criteria (Xue, Bandeen-Roche, et al., 2008). In contrast, exhaustion is thought to manifest later in the frailty cycle, and signals more severe declines in energetics. The current findings suggest that those able to maintain high intellectual and social activity in later life had likely built up sufficient physiologic reserves to buffer against the transition towards more severe criteria of physical frailty (i.e., exhaustion).

We also found that, for the most part, late-life lifestyle engagement did not modify risk trajectories of frailty criteria over time. The main exceptions were for the slow gait and CES-D exhaustion measures, where the benefits of being in the Social Intellectual group declined over time. For slow gait, the risk trajectories for the Social Intellectual and Intellectual groups converged over time, and they had approximately the same average marginal predicted probabilities of slow gait after about 6.5 years. For exhaustion, the risk trajectories between the Social Intellectual and Least Active groups converged over time. Yet, this differential change was small relative to the large baseline difference in exhaustion between these groups. The average marginal predicted probability of exhaustion was still slightly higher in the least active class compared to the most active class even up to 6.5 years later. Mendes de Leon et al. (2003) reported similar findings, where those with the highest social engagement declined faster in functional ability over time, but still had higher functioning throughout the study compared to those with less social engagement.

The lack of longitudinal associations between lifestyle engagement and physical frailty criteria offers several interpretations. First, given the older age-range of our participants, later-life lifestyle engagement may be a proxy for lasting differences in physiologic reserves (i.e., reverse causation). Having sufficient existing physiologic reserves or compensatory mechanisms (e.g., assistive devices, social support) are needed to maintain an intellectually- and socially-

active lifestyle later in the lifespan. Second, later-life lifestyle engagement may help maintain physical functioning, but may do so by delaying, rather than slowing, the etiologic progression of frailty, which is consistent with a reserve perspective (Jack et al., 2013; Xue et al., 2019). This may explain why others have found significant relationships between social engagement and reduced declines in mobility (Buchman et al., 2009) and incident functional disability (Avlund et al., 2004; James, Boyle, Buchman, & Bennett, 2011). Given that physical frailty is considered a preclinical state of vulnerability to future disability (Fried, Tangen, et al., 2001), it is also possible that lifestyle engagement may influence future disability via alternative pathways (e.g., provision of meaningful social roles, social support; Berkman et al., 2000) that encourage maintenance of health without directly acting on the etiology of frailty.

Ultimately, the use of a latent class approach to derive activity groups, presented here may be useful for planning future interventions (Figure 7.1). While differences in number of activities may be important for determining an individual's lifestyle engagement (Carlson et al., 2012), further information on the qualitative differences in types of engagement may help pinpoint novel settings and behaviors to target. Given that there were no differences in risk trajectories over time between lifestyle groups, interventions could focus on supplementing an individual's current lifestyle to specifically target the etiology of physical frailty (Bandeen-Roche et al., 2019). For example, those highly active in social institutional activities (Classes 1 and 2) may be more motivated to participate in a frailty intervention tied to social engagement or nested within a social institution, such as their church or social club. Integrating new interventions into existing activity contexts may ultimately promote more sustainable behavioral changes relevant to prevention of cognitive declines, by directly linking the intervention with

engagement that already gives individuals purpose in life (e.g., Parisi et al., 2015; Varma, Tan, et al., 2016).

There are limitations to the current study. As reported in Aim 1 (Chapter 4.6), we used a retrospective, self-reported inventory to measure activity engagement, which may result in recall bias. We attempted to mitigate recall bias by only using dichotomous (yes/no) activity responses that did not require recall of precise frequencies of engagement. Second, our sample was mostly white participants in a clinical trial, and the current findings warrant further replication and measurement invariance testing in more diverse samples. Third, grip weakness was self-reported in the current study and may be influenced by reporting biases (e.g., recall, social desirability; Gabriel et al., 2012). Yet, such measures have been shown to be valid indicators of physical limitations (Fried, Young, et al., 2001), and may better capture the degree to which weakness has impacted daily tasks (i.e., "enacted" functioning; Glass, 1998). Future research should attempt to replicate our findings with repeated, objective measures of grip strength.

The current study also had several strengths. We used a well-characterized sample of adults at higher age-related risk of cognitive declines. Our sample had strong retention and was well-powered to detect differences in both baseline and longitudinal physical functioning (DeKosky et al., 2006). We also examined physical frailty criteria independently, allowing us to pinpoint potential mechanistic pathways in the relationship between lifestyle engagement and the frailty process. Finally, our novel application of a person-centered LCA approach demonstrated that individuals group naturally by both amount and types of social and cognitive activities, and revealed qualitative differences in engagement that could imply potential motivational differences for staying active in later life. Our study is the first, to our knowledge, to show that these lifestyle engagement groups also differed in risk of baseline frailty criteria.

6.6 Conclusion

Later life provides novel chances for renewed engagement in complex lifestyle activities. The question remains as to whether an engaged lifestyle may help mitigate risk of aging-related physical limitations. Building upon the first two aims of this dissertation, the current findings suggest that higher lifestyle engagement is associated with lower risk of existing physical frailty criteria, but not reduced risk trajectories over time. Nevertheless, lifestyle engagement may still delay incident disability through existing physiologic reserves or through alternative pathways (e.g., purpose in life) that can be explored in future studies. The lifestyle groups included here also provide additional characterization of group-level differences in engagement that are relevant for deploying sustainable interventions to specifically target the frailty process.

Chapter 7: General Discussion and Conclusions

7.1 Summary of Findings

This dissertation examined broad health outcomes associated with distinct lifestyle engagement groups of community-dwelling older adults (Table 1). In Aim 1, we found that a 3- or 4-class model adequately characterized lifestyle engagement in the current sample. We compared these latent class measures to a sum score of activity variety, and found that both predicted risk of incident dementia. Both measures were derived from self-reported inventories of complex later-life activities. The "complexity" of these activities comes from the demands they placed on cognition (including multiple domains), social, and physical functioning broadly, versus specific functional processes (e.g., gait, memory) as in highly controlled behavioral interventions (see Section 2.5).

While the latent classes did not provide additional predictive utility above and beyond the sum score, we found that a latent class approach identified important qualitative differences in types of activity reported between groups. The highly active group (Class 1: Social Intellectual) engaged broadly in intellectual and social activities. Class 2 (Intellectual) was active in specific intellectual (e.g., viewing art, computer use) and social leisure activities (e.g., movies, concerts). Class 3 (Social) was highly active in social institutional activities (e.g., volunteering, church), but less active in intellectual activities. Finally, Class 4 (Least Active) was less active in social and intellectual activities, but still had high likelihood of engagement in certain home-based activities (e.g., reading, gardening). The groups with the highest engagement in intellectual activities (Classes 1 and 2) appeared to have the lowest risk of incident dementia.

Aim 2 extended upon Aim 1 by examining domain-specific cognitive trajectories across the lifestyle engagement groups. We found that groups with higher engagement in intellectual activities (Classes 1 and 2) had greater existing cognitive functioning across domains. Furthermore, compared to the Social Intellectual group (Class 1), the Least Active group (Class 3) had greater annual declines in memory and attention. The Intellectual group (Class 4) had greater declines in visuospatial construction over time compared to the Social Intellectual group (Class 1), despite having equivalent baseline performance in this domain. This aim expanded upon the results of Aim 1 by suggesting that the Social Intellectual and Intellectual groups had reduced risk of incident dementia likely in part through preserved memory performance over time. This aim also revealed additional cognitive benefits of membership in the Social Intellectual group, namely reduced annual declines in memory and attention compared to the Least Active group, and visuospatial construction compared to the Intellectual group.

Aim 3 added to the previous aims by examining whether the benefits of a highly engaged lifestyle extended to certain physical frailty criteria, including slow gait, exhaustion, and grip weakness. The Social Intellectual group (Class 1) had reduced baseline odds of slow gait compared to all other groups, including the Intellectual group (Class 2), for which there were no baseline cognitive differences in Aim 2. Gait speed is an important predictor of mortality (Studenski et al., 2011) and key component of physical frailty (Fried, Tangen, et al., 2001), likely manifesting earlier in the progression of the syndrome (Xue, Bandeen-Roche, et al., 2008). The Social Intellectual group also had reduced odds of exhaustion, but not grip weakness, compared to the Least Active group (Class 4). There were few longitudinal differences between lifestyle groups in the change in risk over time for the physical outcomes. Longitudinal differences for slow gait and CES-D exhaustion were significant. The risk trajectories of slow gait for the Social

Intellectual and Intellectual groups converged over time, whereas for CES-D exhaustion the trajectories for the Social Intellectual and Least Active groups converged over time. Together, this evidence suggested that high lifestyle engagement is likely associated with existing physical reserves through preserved lower-extremity mobility. Yet, high lifestyle engagement was not associated with attenuated risk of physical frailty outcomes over time, suggesting that later-life lifestyle engagement may not act directly on the etiology of physical frailty.

7.2 General Discussion and Connections

When interpreted together, the findings from the three aims of this dissertation provide important insights into how high lifestyle engagement may contribute to better health in older adulthood and which components of that engagement seem to drive the relationships. Furthermore, these findings have implications for specific group-level interventions aimed to complement existing lifestyle contexts. These interventions could ideally provide targeted benefits while also encouraging sustained participation through linkage to activities that older adults already engage in.

7.2.1 Intellectual activity and cognitive health. One challenge of using lifestyle activity inventories is classifying activities into specific subdomains (i.e., intellectual, social, etc.), because these activities are complex and incorporate a mix of motor, cognitive, and social engagement. Classification is often done *a priori*, but here we used a latent class approach to categorize the individuals themselves rather than the activities, given that individuals are likely to have activities in common across subdomains. This complementary approach led us to find that those reporting a high quantity of activities are also more likely to report more intellectual activities (e.g., taking courses, viewing art). This agrees with the observed data, as the

intellectual activities were some of the least frequently reported activities in this sample. Yet, the latent class approach also revealed an intermediate class (Class 2: Intellectual) with high engagement in only specific intellectual activities (e.g., viewing art, computer use) and less relative engagement in social institutional activities (e.g., volunteering), suggesting that high social or community engagement is not a prerequisite for intellectual engagement.

Ultimately, there was almost no difference in risk of incident dementia, as well as baseline and annual changes of domain-specific cognitive performance between the Social Intellectual and Intellectual groups, both of which had higher intellectual engagement. In contrast, the groups with high social engagement only (Class 3: Social) and lower overall engagement (Class 4: Least active) had higher risk and higher declines in these outcomes. This suggests that those engaged in intellectual activities into later life are likely the best equipped to mitigate age-related cognitive declines and incident cognitive impairment. This agrees with the enrichment hypothesis (Hertzog et al., 2009), which suggests that high intellectual engagement in later-life is not only associated with greater existing brain and cognitive reserves (Stern, 2002) that could delay impairment, but also actively attenuates future declines. Other studies have also found that high intellectual engagement is particularly protective against dementia (Scarmeas et al., 2001) and cognitive declines (Bielak, 2010; Carlson et al., 2012; Gow et al., 2014).

7.2.2 Social activity and physical health. In contrast to the findings for cognitive outcomes (Aims 1 and 2), social activity appeared to play an important role in existing physical health for the current sample (Aim 3). The primary difference between the groups with the most intellectual activity was their level of social engagement. The Social Intellectual group (Class 1) was more likely to report participation in social institutional activities, as well as intellectual activities with a social component (e.g., singing, courses), than the Intellectual group (Class 2).

In Aim 3, we found that the Social Intellectual group had reduced risk of existing slow gait compared to all other groups. We further found that the Social group (Class 3) had relative odds of slow gait and exhaustion at baseline that were comparable to the Intellectual group (Class 2), suggesting minimal differences between these groups in existing physical impairments. Together, these findings suggest that the addition of social institutional activities to an intellectually-active lifestyle is an important correlate of higher physical reserves in later life. This relationship may be mediated in part by life-space mobility, where higher community engagement encourages expanded physical activity within one's environment (Rosso, Taylor, et al., 2013). Again, because we found minimal longitudinal differences across groups, reverse causation could also play a role here, where those with high existing physical reserves have the capacity to be more intellectually and socially active in later life.

7.2.3 Social institutions as a setting for universal interventions. One advantage of the current approach is that it identified a group with high social institutional engagement (Class 3: Social) despite having relatively poorer physical and cognitive health. This suggests that a certain level of "real-world" functioning that contributes to an individual's quality of life is preserved despite prevalent physical and cognitive limitations. Discrepancy between lab-measured, "experimental" functioning and daily-life, "enacted" functioning has also been found in other studies of activity engagement (Glass, 1998).

The identification of the Social group has important implications for prevention, because it suggests that the social institutions measured here may be important settings to deploy *universal interventions*. Unlike *selective* and *indicated* interventions, *universal* interventions are delivered to individuals regardless of their risk level, and focus on the institutions broadly relevant to individuals of various levels of functioning (Gordon, 1983). From this study, settings

for group-level universal interventions could include churches, social clubs, and volunteer groups; where some older adults with relatively poorer physical and cognitive health outcomes spend their time. Provided it is feasible and non-stigmatizing, a nested approach could also be used (Haggerty & Mrazek, 1994), where individuals are first screened, and those of higher risk are offered more targeted interventions. A broader framework and content of potential interventions is included in Table 7.1 and in the "Future Directions" section below.

7.2.4 Mechanism and timing for the lifestyle-health relationship. Although no causal conclusions can be drawn from the current associational findings, they provide insight into potential mechanistic pathways and timing by which lifestyle engagement may act on cognitive and physical health. We found significant longitudinal benefits for cognitive, but not physical outcomes. Thus, it may be that late-life lifestyle engagement protects against cognitive impairment through brain (i.e., passive) and cognitive (i.e., active) reserve pathways (Bennett et al., 2014; Stern, 2002), rather than by directly mitigating inflammation or other shared pathology between cognitive impairment and physical frailty (Xue et al., 2019). This agrees with prior research that found that most indicators of an engaged lifestyle, such as social activity, were associated with better cognitive functioning, but not through reductions in brain pathology (e.g., beta amyloid accumulation; Bennett et al., 2014).

Furthermore, lifestyle is a complicated behavioral construct that includes not only leisure activity, but also other general health behaviors that can influence health in later life (e.g., smoking, diet). The strongest observational evidence for an association between lifestyle and physical frailty has been through diet and physical exercise (Ferrucci & Fabbri, 2018). These behaviors are thought to directly attenuate inflammation and accumulation of oxidative stress (Xue et al., 2019). Given that our lifestyle engagement measure included mostly intellectual and

social activities with less emphasis on physical activity and diet, it may ultimately not be surprising that we found no longitudinal benefits of late-life lifestyle engagement on physical frailty criteria if inflammation is an important etiological component.

However, timing is another important consideration. We measured lifestyle engagement in later-life, where participants were about 78 years old, on average. Other studies have reported that leisure activity in later life had less of a protective association than leisure activity in mid- or early-life (Gow et al., 2017). Lifestyle engagement measured in later life may just represent existing physiologic reserves, whereas lifestyle engagement in midlife or earlier in older adulthood could actively mitigate future physical declines (see "Future Directions"), especially considering that early indicators of physical frailty may start appearing in midlife (Xue, Bandeen-Roche, et al., 2008). However, that is not to say that lifestyle engagement in later life is not an important protective factor, as evidenced by our findings for dementia and domain-specific cognition. Even well into older adulthood, leading an intellectually- and socially-complex lifestyle appears to attenuate declines in memory, attention, and visuospatial abilities essential to living independently and maintaining a high quality of life (Berkman et al., 1993; Rowe & Kahn, 1997; Zahodne et al., 2013).

7.3 Limitations

7.3.1 Limitations with latent class analysis. Sample size and sparseness of response patterns can limit the estimability of latent class models (Collins & Lanza, 2010). The relatively large number of indicators available in the Lifestyle Activity Questionnaire (LAQ) in the current study led to sparse response patterns and required us to choose a subset of 18 activities to include in the model.

Yet, we approached this using both an empirical and theoretical rationale, removing activities with very high (e.g., watching TV) or low (e.g., hunting) frequencies in the current sample, and those that were considered "passive" (e.g., radio listening) or confounded with IADL or ADL measures (e.g., shopping). We also recoded the activity measures as binary (yes/no) responses, both to capture activity variety (Carlson et al., 2012) and reduce sparseness in response patterns from using the frequency measures. Finally, we further examined the sensitivity of class enumeration to specific activities by repeating the LCA with subsets of nine activities chosen semi-randomly (i.e., 4 intellectual, 1 physical, 4 social). Doing so revealed variation in the class number across subsets, but suggested that a 3- or 4-class model generally fit best and without convergence errors.

7.3.2 Retrospective self-reported activity measure. Despite being designed to measure easily-recalled, common lifestyle activities, the retrospective nature of the LAQ may lead to recall bias. A major concern is the accuracy with which individuals can report precise frequencies of activity engagement (Bielak, 2017). This concern is mitigated for three reasons. First, as mentioned above, frequency items were recoded such that participants only had to indicate whether or not they had participated in that activity at least once per month during the year. Furthermore, retrospective recall can be very accurate even for adults over 50 years old (Berney & Blane, 1997). Finally, retrospectively reported activities have been shown to have high test-retest reliability (ICC>.8) in a prior study of older adults (Schreiber et al., 2016).

A further limitation of the LAQ and most self-reported activity questionnaires is that they cannot capture the intensity or quality with which individuals do activities. For example, someone who reports doing crossword puzzles does not necessarily do them well, and someone who reports attending church may go for just the service, without significant social engagement

or integration within the congregation. The intensity with which individuals are active can be difficult to capture in self-reported measures, due to individual differences in what constitutes "intense" or effortful engagement, although some have tried to measure it (e.g., activity characteristic measures; Bielak, 2017).

Wearable devices or smart phones that measure daily activity with more ecological validity may offer one solution to the above limitations. Accelerometer- and GPS-enabled devices are increasingly being used to objectively measure physical activity and life-space mobility, even within older adult populations (Heesch et al., 2018; Kerr et al., 2013; Varma et al., 2014). Smart phones are also being used for ecological momentary assessments (EMA) of cognition (Sliwinski et al., 2018), as well as stress, mood, and other psychological constructs that are especially vulnerable to recall bias (Shiffman et al., 2008; Steptoe & Wardle, 2011). One important future direction may be to integrate these data collection sources to better measure the physical (via accelerometry), social (via GPS), and cognitive/psychological (via EMA) components of daily activities to provide insight into the intensity or quality of engagement in later-life.

7.3.3 Generalizability of the GEM sample. The GEM sample was composed of primarily white older adults who met the level of functioning necessary to be eligible for a rigorous clinical trial. This included being dementia-free at baseline, having a specific medical history, and being able to participate in an extensive neuropsychological battery and repeated assessments.

Yet, specific steps were taken by the original investigators to improve generalizability. Most importantly, they did not exclude individuals with prevalent MCI, allowing for more variability in the level of baseline cognitive performance in this sample (DeKosky et al., 2006).

Nevertheless, future studies should replicate these results in more representative cohorts, as detailed in the "Future Directions" section.

7.4 Strengths

7.4.1 GEM study design. GEM participants were well-characterized at baseline and of an older mean age, making it an appropriate sample to investigate later-life activity engagement. GEM was also well-powered to detect longitudinal changes in cognitive and physical outcomes given its relatively large sample size. Median follow-up was about six years for cognitive and physical outcomes, with dementia screening occurring relatively frequently at six-month intervals. Furthermore, dementia was clinically-adjudicated using gold-standard diagnostic criteria derived from standardized neuropsychological testing, MRI, and a clinical neurological examination.

7.4.2 Analytical approach. We used a rigorous analytical approach to examine each study aim. For the cognitive and physical outcomes, we employed longitudinal mixed effects modeling approaches that utilized all the available observed data and were robust to data missing at random. In aim 2, we derived domain-specific cognitive measures from several neuropsychological tests that provided more precise estimates of these domains than if just a single test was used. In aim 3, we included both objective and perceived measures of physical frailty criteria, and examining these criteria individually allowed us to determine how lifestyle may influence specific components of the frailty phenotype. Finally, we used a novel, latent class approach to examine how older adults may group based on quantitative and qualitative differences in lifestyle engagement. Group differences in types of activities may be especially important for designing group-level activity interventions that motivate individuals to stay active (see "Future Directions" below).

7.4.3 Addressed gaps in the literature. Finally, all three aims of this dissertation added to the existing literature in unique ways. To our knowledge, Aim 1 was the first study that compared the predictive utility of a simple sum score of activity variety with a more complex latent class approach. Ultimately, both approaches predicted incident dementia, but both may fulfill a unique role depending on the study objective (i.e., sum score for prediction models, latent class indicator for additional lifestyle characterization). Aim 2 also was among the first studies to explore how latent groups of lifestyle engagement predicted domain-specific cognitive outcomes, and found differences in both baseline and trajectories of performance for select domains. Finally, aim 3 is among the first studies to explore how engagement in broad lifestyle activities may be related to various components of the physical frailty cycle. Together, findings from these latter two aims suggest that later-life lifestyle engagement is associated more so with cognitive than physical functioning trajectories. Yet, high activity appears to be associated with both high existing cognitive and physical performance.

7.5 Future Directions

The collective work in this dissertation offers several avenues for future study. I focus on three potential future directions below.

7.5.1 Generalizability of the construct. Future studies can attempt to validate the latent classes characterized here within other studies with diverse samples. Variation in measurement of lifestyle engagement groups could occur at the construct-level (i.e., measurement invariance; is the 4-class model sufficient in novel samples?) or at the item-level (i.e., differential item functioning; do items perform differently for certain subpopulations, independent of their latent class membership?; Collins & Lanza, 2010). For example, some have found that African

Americans and those of lower socioeconomic status (SES) report visiting museums less than white or higher income individuals, suggesting that this activity may not adequately capture lifestyle engagement in these groups (Schinka et al., 2005). "Viewing art" was likely the closest analog to "visiting museums" in our study, but was intended to be interpreted broadly rather than only as viewing art at a museum. Nevertheless, teasing apart these issues of measurement would help clarify the degree of heterogeneity in lifestyle engagement between populations, and whether there are specific activity selections in subpopulations that are relevant for prevention efforts.

7.5.2 Lifespan perspective. Early life activity has been found to be an independent predictor of both future activity and neurocognitive functioning in older adulthood (Chan et al., 2018; Gow et al., 2017; Moored et al., 2018). Given this, it would be beneficial for future work to explore how lifestyle engagement manifests in younger age groups, potentially using a similar latent class approach as used here. It is currently unknown whether younger individuals group by similar patterns of intellectual and social engagement as do older individuals.

Furthermore, it is crucial to understand modifiable lifespan predictors of later-life lifestyle engagement, given that there were large baseline differences in cognitive and physical functioning between the lifestyle groups in the current study. Exploration of psychosocial (e.g., purpose in life, social supports) and behavioral (e.g., health maintenance) predictors could inform how older adults remain active into later life to build these physical and cognitive reserves, and provide early prevention targets to sustain complex activity throughout the lifespan.

7.5.3 Later-life interventions. Finally, our characterization of lifestyle engagement groups and findings for how these groups differ in current and future health have implications for intervention. Interventions could focus either on ***maintaining*** or ***supplementing*** existing lifestyle

activity (Figure 7.1). Given that those in the Social Intellectual group had higher baseline cognitive and physical functioning, as well as better cognitive functioning over time, interventions within this group could focus on ***maintaining*** current activity levels by providing intrinsic (e.g., assistive devices) or extrinsic (e.g., social supports/assistance) compensatory mechanisms (Xue, Fried, et al., 2008).

Yet, we also observed that the intermediate groups (e.g., Class 3: Social) were at higher risk for existing and future health declines compared to the most active group. These groups may benefit from a ***supplemental*** approach, where interventions that encourage additional health-promoting activity can be nested within their existing lifestyle context. For example, those in the Social group (Class 3) may benefit from an intervention like Experience Corps, which was nested within a highly social context (i.e., volunteering at schools in the Baltimore community). In contrast, those in the Least Active class who were less social (Class 4) may benefit from a home-based intervention encouraging both physical and cognitive engagement. *Bandit the Dolphin* is one such intervention currently being tested within a retirement community in Catonsville, MD (Carlson et al., in preparation). This intervention encourages cognitive-motor integration through a fun, motion-tracking video game. Although it may not appeal to everyone, its portability provides opportunities to deploy as a home-based platform for those who are not heavily active in their community.

While the above ***supplemental*** approach aims matches specific interventions to lifestyle groups, the current findings may also inform how to improve adherence in more general-purpose interventions. For example, the FINGER trail was a large-scale intervention that targeted the three key prevention areas for cognitive decline detailed earlier in this dissertation: physical exercise, cognitive training, and nutritional monitoring (Ngandu et al., 2015). The study found

modest post-intervention benefits for select cognitive domains in intention-to-treat analyses. Yet, low adherence potentially influenced these findings. For cognitive training, 33% of participants attended only up to half of the 144 individual sessions, and 37% attended none (Supplemental Table 6). Furthermore, about a quarter of participants did not record any gym training sessions over the 2-year study period. Like the Least Active group in the current study, these individuals may have benefitted from additional resources (e.g., case manager, home-based alternatives) that may have provided the scaffolding necessary to modify their health behaviors. Building the self-efficacy to complete such activities in a safe, supportive environment may have encouraged these individuals to maintain engagement and build up to attempting these activities in the community settings where they were originally administered (Booth et al., 2000).

Ultimately, the extent to which this approach of triaging individuals or designing behavioral interventions based existing lifestyle profiles warrants testing in future studies. Doing so could provide a novel framework for group-level intervention design and deployment that could maximally benefit public health stakeholders and older adults themselves. Maintaining an active lifestyle is one key to living well in later life (National Academies of Sciences, Engineering, and Medicine, 2017). It is therefore crucial that we provide older adults with accessible, sustainable, and engaging opportunities that may ultimately have enriching effects on their health for years to come.

Figure 1.1: Theoretical framework for how lifestyle activity patterns relate to cognitive and mobility outcomes

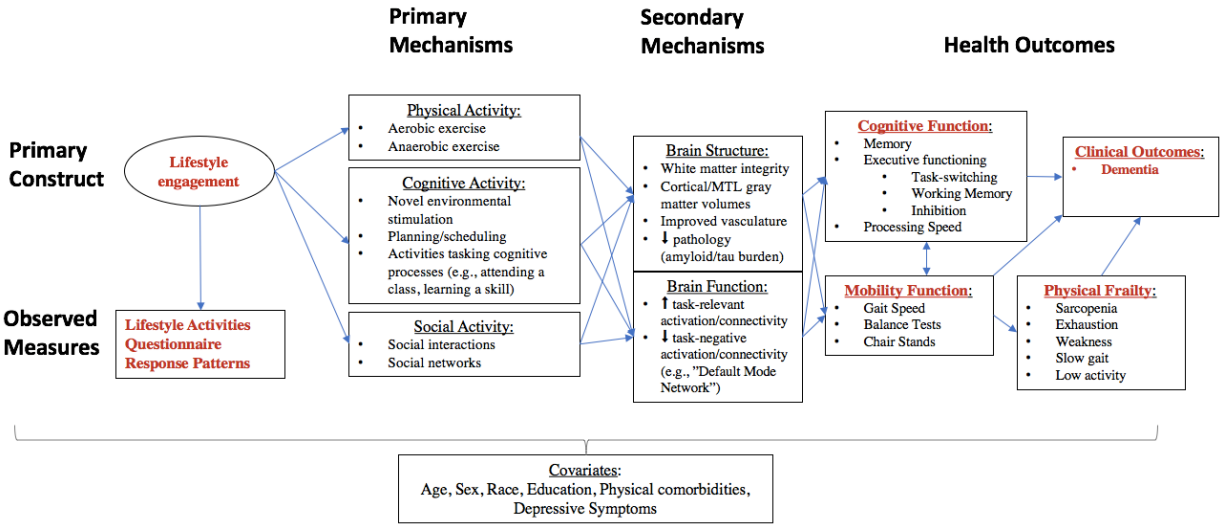
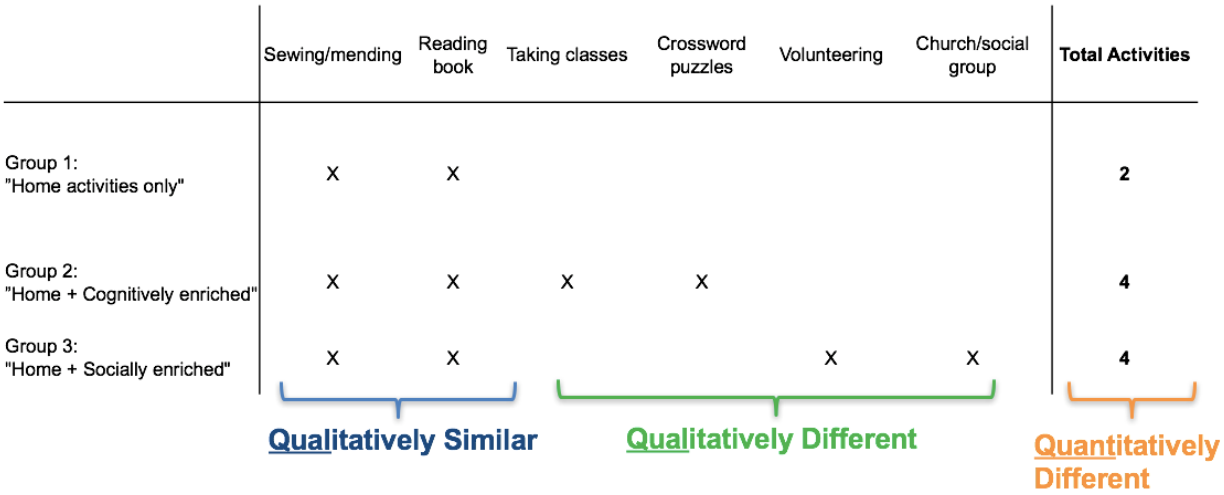


Figure 1.2: Hypothetical example illustrating potential qualitative and quantitative differences contributing to underlying heterogeneity in lifestyle engagement



Note: Activities commonly reported within each latent group are indicated by an "X." Total number of activities commonly reported by each group are displayed in the right-most column. All groups report doing common activities at home (e.g., sewing/mending, reading books). Groups 2 and 3 both have four activities that they report with high probability. Individuals in Group 2 more commonly report taking classes or doing crossword puzzles (i.e., "cognitive" activities), while individuals in Group 3 more commonly report volunteering and membership in a church/social group (i.e., "social" activities). In contrast, individuals in Group 1 commonly report a fewer number of activities, and they are more restricted to the home environment.

Figure 1.3: Simplified theoretical framework including current aims

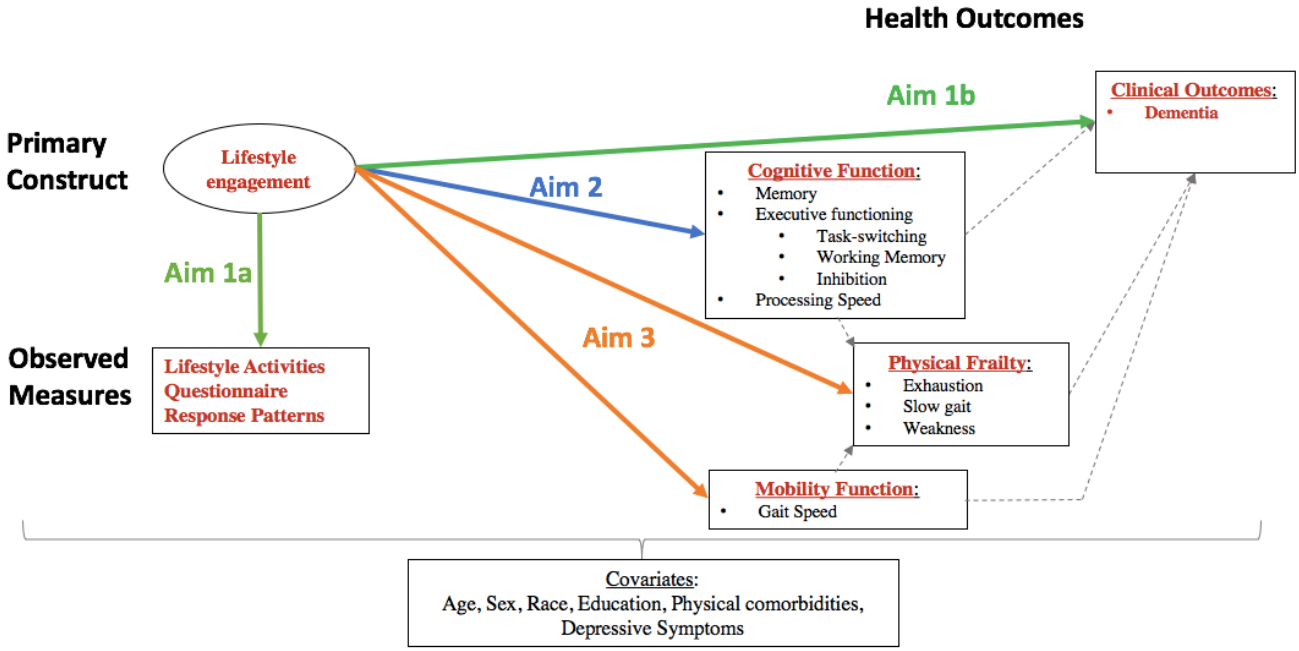
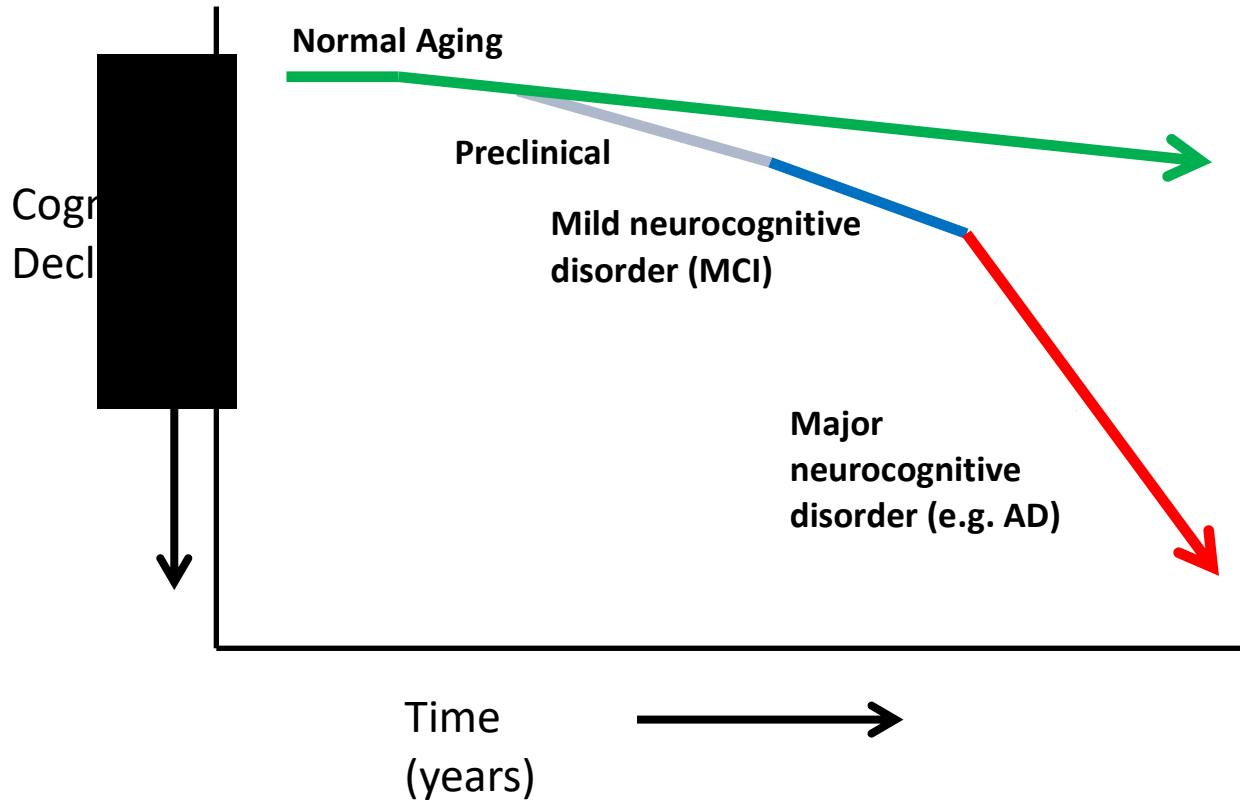


Table 2.1: Operationalization of the frailty phenotype in the Cardiovascular Health Study

Frailty Characteristic	Observed Measure indicating Frailty
Weight loss	Unintentional weight loss of at least 5% of previous year's body weight
Exhaustion	Two items of the CES-D. Reported feeling that "everything they did was an effort" or "I could not get going" at least moderate amount of time during the past week.
Low physical activity	Minnesota Leisure Time Activity Questionnaire (short form) using standardized algorithm for calculating Kcals of activity per week and stratifying by sex. Men: <383 Kcals per week Women: <270 Kcals per week
Slow walking time	Time to walk 15 feet at usual pace, stratified by sex and height: <u>Men</u>: Height ≤ 173 cm, walking time ≥ 7 sec. Height > 173 cm, walking time ≥ 6 sec. <u>Women</u>: Height ≤ 159 cm, walking time ≥ 7 sec. Height > 159 cm, walking time ≥ 6 sec.
Weakness	Grip strength stratified by sex and body mass index: <u>Men</u>: BMI ≤ 24, grip strength ≤ 29 BMI 24.1–26, grip strength ≤ 30 BMI 26.1–28, grip strength ≤ 30 BMI > 28, grip strength ≤ 32 <u>Women</u>: BMI ≤ 23, grip strength ≤ 17 BMI 23.1–26, grip strength ≤ 17.3

	BMI 26.1–29, grip strength ≤ 18 BMI > 29, grip strength ≤ 21

Figure 2.1: Progression from “normal” aging to major neurocognitive disorder



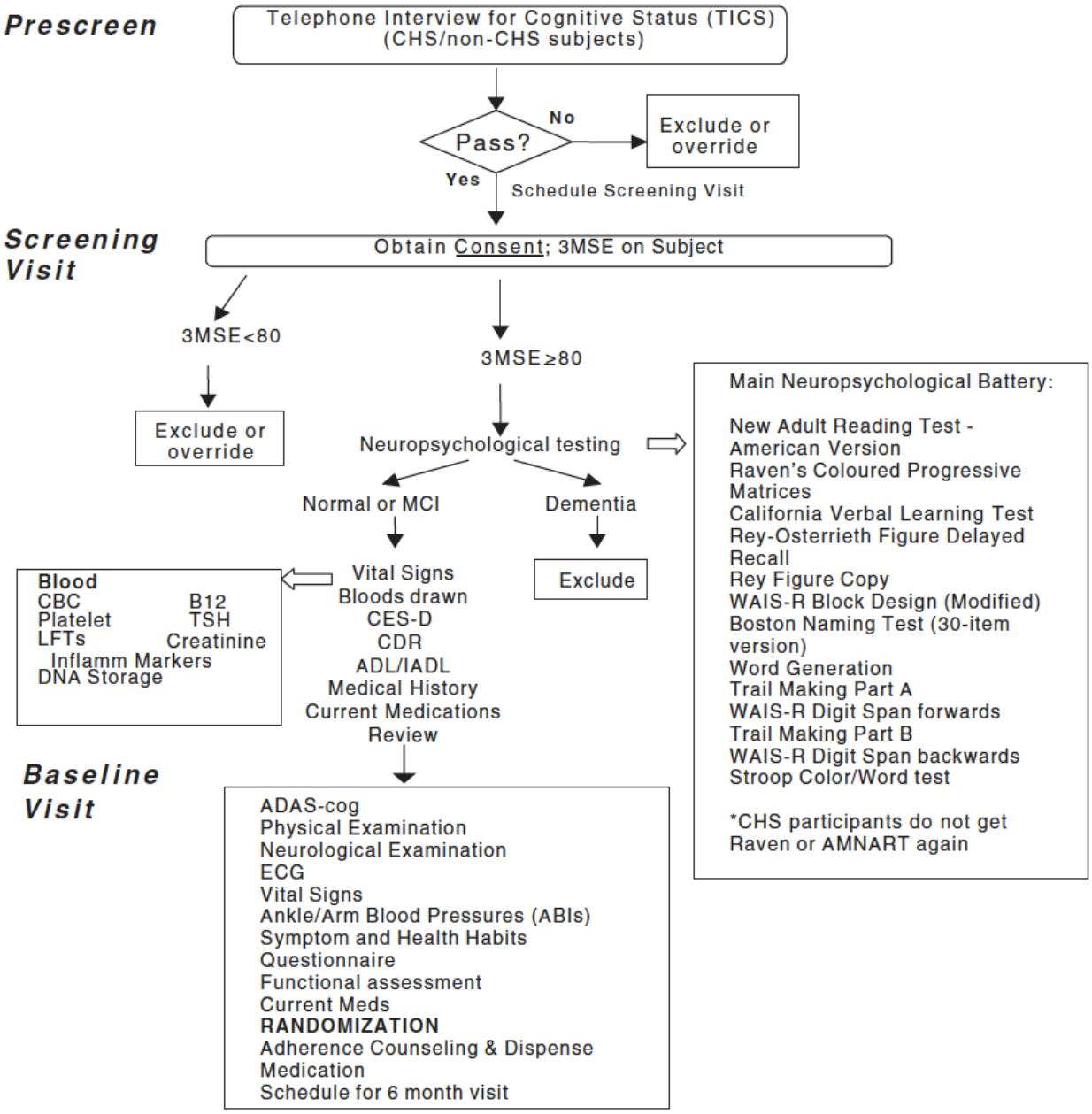
Adapted from Institute for Memory Impairments and Neurological Disorders, University of California Irvine [http://www.mind.uci.edu/dementia/mild-cognitive-impairment/

Table 3.1: Ginkgo Evaluation of Memory Study Neuropsychological Test Battery (GEM NTB) for adjudication of cognitive impairments

Domain	Subdomain	Observed Measure
Memory	Verbal Learning	California Verbal Learning Test (Immediate Free Recall) [a]
	Verbal Episodic Memory	California Verbal Learning Test (Long Delayed Free Recall)
	Visual Episodic Memory	Rey-Osterrieth Complex Figure (Delayed Recall)
Visuospatial Construction		Rey-Osterrieth Complex Figure (Copy Condition)
		Wechsler Adult Intelligence Scale-Revised (WAIS-R) Block Design
Language		Boston Naming Test
		Animal Fluency
Attention/ Psychomotor Speed		Trail Making Test Part A (time in seconds)
		WAIS-R digit span forwards (total score)
Executive Functioning	Task-switching	Trail Making Test Part B (adjusting for Part A)
	Inhibition	Stroop Color/Word Test (Interference condition, number of colors named)
	Working Memory	WAIS-R digit span backwards (total score) [a]
Intelligence	Crystalized	National Adult Reading Test – American version [b]
	Fluid	Raven's Progressive Matrices (colored) [b]

Note. [a] administered but not used in adjudication of cognitive impairments
[b] administered at baseline only

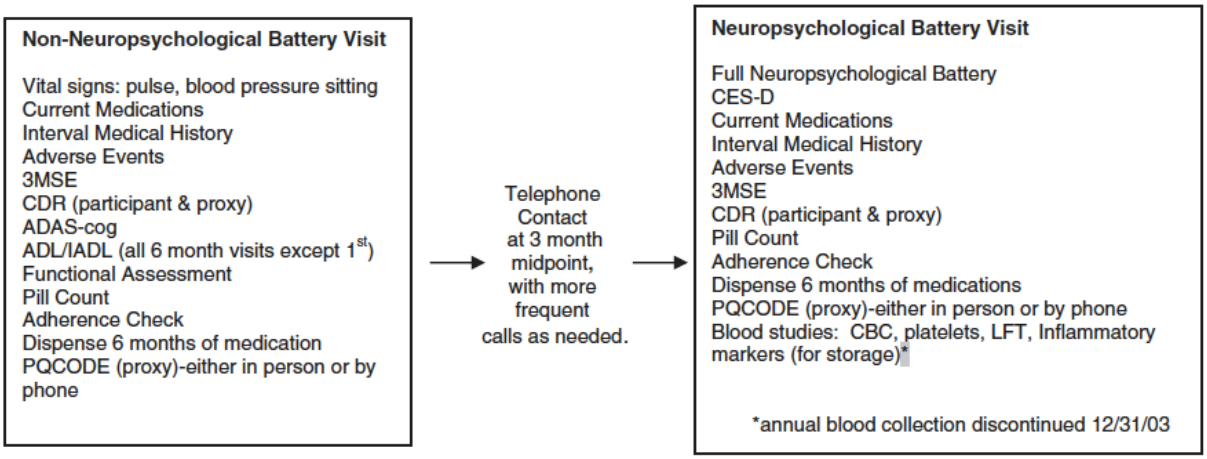
Figure 3.1: GEM screening and baseline procedures (from DeKosky et al., 2006)



Note. CHS = Cardiovascular Health Study, 3MSE = Modified Mini-Mental State Exam, MCI = Mild Cognitive Impairment, WAIS-R = Wechsler Adult Intelligence Scale – Revised, CBC = complete blood count, B12 = Vitamin B12, TSH = Thyroid Stimulating Hormone, LFTs = liver function tests, CES-D = Centers for Epidemiologic Studies Depression Scale, ADL = activity of

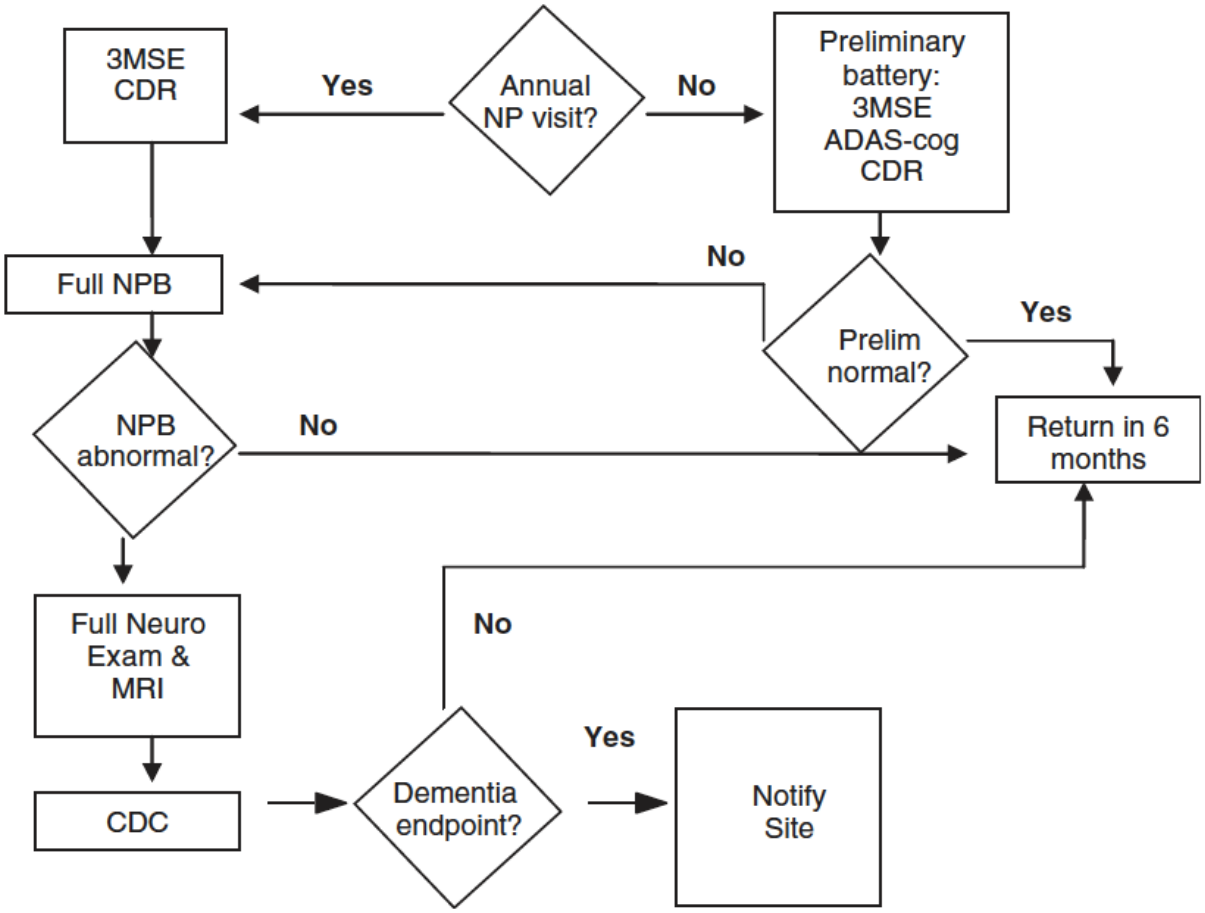
daily living, IADL = instrumental activity of daily living, ADAS-Cog = Alzheimer's Disease Assessment Scale - Cognitive Subscale, ECG = electrocardiogram, ABI = ankle brachial indices

Figure 3.2: GEM six-month and annual visits (from DeKosky et al., 2006)



Note. 3MSE = Modified Mini-Mental State Exam, CDR = Clinical Dementia Rating Scale, ADAS-Cog = Alzheimer's Disease Assessment Scale - Cognitive Subscale, CES-D = Centers for Epidemiologic Studies Depression Scale, ADL = activity of daily living, IADL = instrumental activity of daily living, PQCODE = Proxy Questionnaire for Cognitive Decline in the Elderly

Figure 3.3: GEM Dementia Adjudication Procedure (from DeKosky et al., 2006)



Note. NP visit = neuropsychological test visit, 3MSE = Modified Mini-Mental State Exam, CDR = Clinical Dementia Rating Scale, ADAS-Cog = Alzheimer's Disease Assessment Scale - Cognitive Subscale, NPB = GEM Neuropsychological Test Battery

Table 4.1: Frequency of self-reported Lifestyle Activity Questionnaire activities over the past year

	Parisi et al. (2012) Domain Category	Proportion Participating At Least Once a Month		Reason(s) removed
		N	Percent	
Selected Activities				
Reading a book	Intellectual	2,545	82.9	
Walking	Physical	2,526	82.3	
Gardening	Physical	2,262	73.7	
Assist family	Social	2,250	73.3	
Attend church/religious service	Social	2,248	73.2	
Clubs/organizations	Social	2,241	73.0	
Sewing, mending, fixing things	Creative	2,220	72.3	
Volunteering	Social	1,749	57.0	
Playing cards or games	Social	1,535	50.0	
Using computer	Intellectual	1,247	40.6	
View art	Creative	1,167	38.0	
Crossword puzzles	Intellectual	1,141	37.2	
Going to plays/concerts	Social	1,127	36.7	
Singing, playing instrument	Creative	1,023	33.3	
Babysitting	Social	943	30.7	
Movies	Social	867	28.2	
Taking courses	Social	521	17.0	
Drawing or painting	Creative	344	11.2	
Removed Activities				
Watching TV	Passive	3,021	98.4	High frequency, passive
Shopping	Physical	3,004	97.9	High frequency, IADL
Reading a newspaper	Intellectual	2,984	97.2	High frequency
Discussing local or national issues	Social	2,881	93.8	High frequency
Visiting others	Social	2,844	92.6	High frequency
Listening to radio (music)	Passive	2,787	90.8	High frequency, passive
Balancing checkbook	Intellectual	2,423	78.9	IADL
Listening to radio (not music)	Passive	2,416	78.7	Passive
Cooking/preparing food	Creative	2,313	75.3	IADL
Hunting/camping	Physical	274	8.9	Low frequency

Note. IADL = instrumental activity of daily living

Table 4.2: Sample characteristics (N=3,068)

	Overall			Class 1: Social Intellectual (n=662)		Class 2: Intellectual (n=514)		Class 3: Social (n=1,036)		Class 4: Least Active (n=856)		
	N (or M)	% (or SD)	Range	N (or M)	% (or SD)	N (or M)	% (or SD)	N (or M)	% (or SD)	N (or M)	% (or SD)	P-value
Site												
Wake Forest	732	24		194	29	89	17	284	27	165	19	<.001
UC Davis	914	30		188	28	192	37	259	25	275	32	
Johns Hopkins	456	15		81	12	36	7	189	18	150	18	
Pittsburgh	966	31		199	30	197	38	304	29	266	31	
Age	78.5	3.3	72-96	78.1	3.1	78.2	3.0	78.7	3.2	78.9	3.6	<.001
Sex (male)	1,649	54		294	44	273	53	567	55	515	60	<.001
Race (white)	2,929	95		637	96	500	97	985	95	807	94	0.047
Education												
<=HS	1,103	36		137	21	97	19	461	45	408	48	<.001
some college	775	25		180	27	138	27	244	24	213	25	
college grad	480	16		107	16	114	22	138	13	121	14	
professional/grad	710	23		238	36	165	32	193	19	114	13	
Mild Cognitive Impairment	481	16		78	11.78	50	9.73	171	16.51	182	21	<.001
Medical Comorbidities	1.4	1.1	0-7	1.3	1.0	1.4	1.0	1.3	1.0	1.6	1.1	<.001
Depressive Symptoms (CES-D)	3.6	3.5	0-6	3.2	3.0	3.7	3.7	3.5	3.5	4.0	3.7	<.001

Note. P-values are for ANOVAs (continuous variables) and chi-square tests (categorical variables) of differences between lifestyle groups.

Table 4.3: Fit statistics for class enumeration

	No. of classes				
	2	3	4	5	6
No. of parameters	37	56	75	94	113
Log-likelihood	-30256	-29994	-29811	-29681	-29621
AIC	60587	60099	59773	59550	59468
BIC	60810	60437	60225	60117	60149
N-adjusted BIC	60692	60259	59987	59818	59790
LMR/BLRT null hypothesis	1 vs. 2	2 vs. 3	3 vs. 4	4 vs. 5	5 vs. 6
LMR p-value	<.001	<.001	0.061	0.399	0.351
BLRT p-value	<.001	<.001	<.001	<.001	<.001
Entropy	0.637	0.626	0.621	0.625	0.605

Note. No. = number, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, LMR = Lo-Mendell-Rubin test, Prop. = proportion. The LMR and BLRT null hypothesis is that a model of *k* classes does not fit significantly better than a model of *k-1* classes.

Table 4.4: Unadjusted and adjusted discrete-time proportional hazards models for activity variety predicting time to dementia

	Model 1 (Unadjusted)			Model 2 (Adjusted)			Model 3 (stratified by MCI)					
							Non-MCI (n=2,587)			MCI (n=481)		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Activity variety (count)	0.916	(.89,.94)	<.001***	0.933	(.91,.96)	<.001***	0.936	(.90,.97)	0.001**	1.006	(.96,1.06)	0.808
Age				1.208	(1.14,1.28)	<.001***	1.198	(1.12,1.29)	<.001***	1.168	(1.06,1.29)	0.003**
Age >80				0.927	(.83,1.03)	0.177	0.927	(.80,1.07)	0.291	0.901	(.75,1.08)	0.264
Age >85				0.849	(.70,1.03)	0.092	0.816	(.62,1.07)	0.135	1.037	(.79,1.36)	0.791
Age >90				1.483	(.97,2.26)	0.066	1.809	(.99,3.29)	0.053	0.928	(.52,1.65)	0.801
Sex (male)				0.819	(.68,.98)	0.030*	0.813	(.65,1.02)	0.074	0.885	(.65,1.21)	0.440
Race (non-white)				1.484	(1.03,2.14)	0.034*	1.055	(.57,1.94)	0.863	0.952	(.59,1.53)	0.838
Education (ref: <=HS)												
Some college				0.930	(.74,1.17)	0.535	0.953	(.71,1.28)	0.751	0.632	(.43,.93)	0.019*
College graduate				0.960	(.73,1.26)	0.772	1.026	(.73,1.43)	0.879	1.067	(.65,1.76)	0.800
Professional/Graduate Degree				1.219	(.96,1.54)	0.099	1.237	(.91,1.68)	0.170	0.750	(.51,1.11)	0.149
Study Site (ref: Wake Forest)												
UC Davis				0.887	(.70,1.12)	0.316	1.020	(.75,1.39)	0.901	1.135	(.78,1.65)	0.508
Johns Hopkins				1.067	(.81,1.40)	0.637	1.203	(.85,1.71)	0.302	1.153	(.74,1.79)	0.528
Pittsburgh				0.672	(.52,.86)	0.002**	0.742	(.54,1.03)	0.074	0.738	(.50,1.09)	0.128
Treatment group				1.107	(.93,1.32)	0.249	1.031	(.83,1.28)	0.786	1.096	(.82,1.46)	0.533
Medical comorbidities				1.102	(1.02,1.19)	0.014*	1.161	(1.05,1.28)	0.003**	1.017	(.89,1.16)	0.800
Depressive symptoms (CES-D>=10)				1.735	(1.32,2.29)	<.001***	1.936	(1.36,2.76)	<.001***	1.019	(.65,1.60)	0.933
Model AUC			0.6878			0.7414						

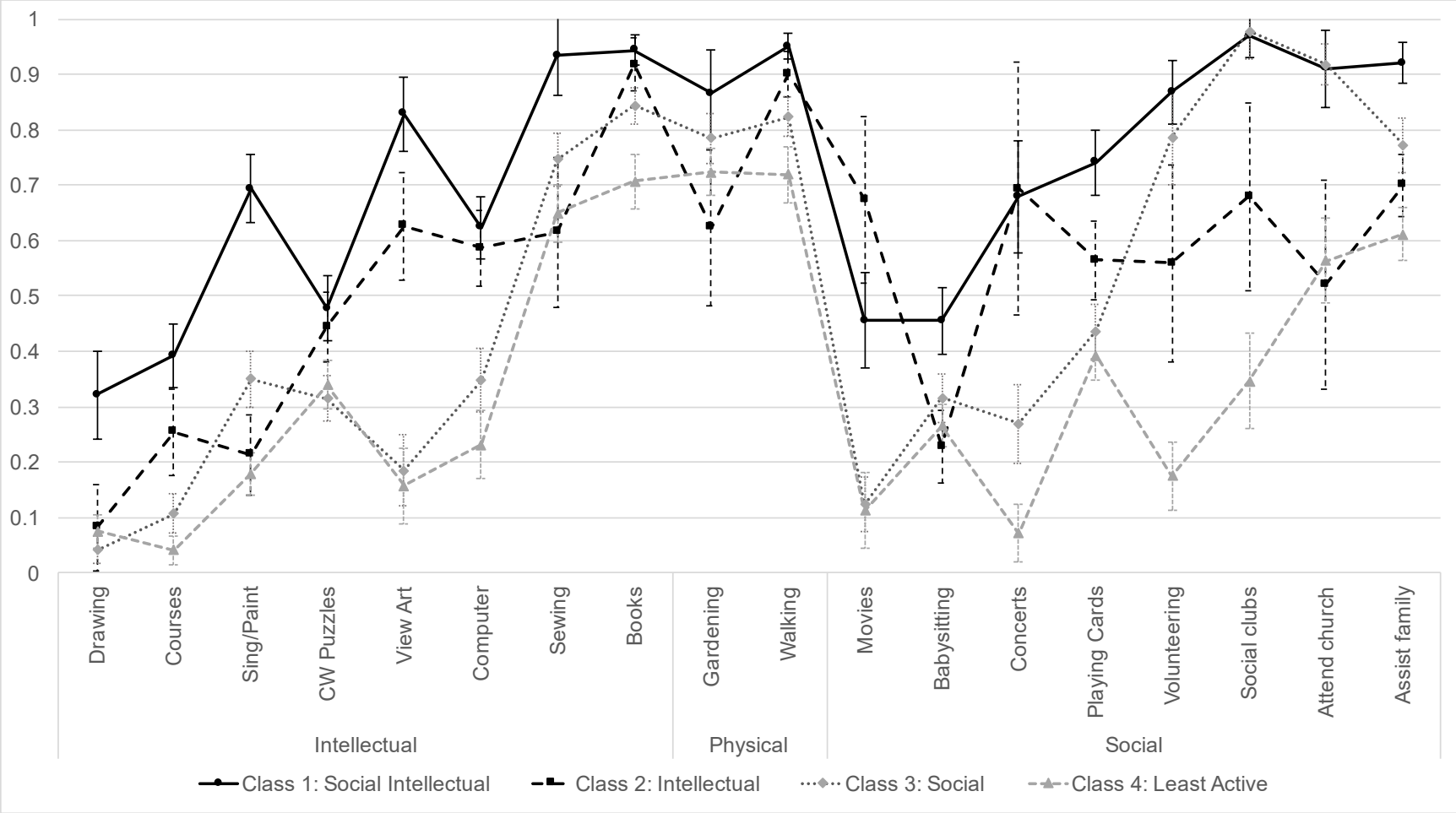
Note: $p<.05$*, $p<.01$**, $p<.001$***. MCI = Mild Cognitive Impairment, HS = high school. Model 1 is unadjusted for covariates. Model 2 is adjusted for demographic and health covariates. Model 3 is stratified by MCI status.

Table 4.5: Unadjusted and adjusted discrete-time proportional hazards models for lifestyle classes predicting time to dementia

	Model 1 (Unadjusted)			Model 2 (Adjusted)			Model 3 (stratified by MCI)					
							Non-MCI (n=2,587)			MCI (n=481)		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Lifestyle engagement group (Ref: Class 1: Social Intellectual)												
Class 2: Intellectual	0.906	(.66,1.24)	0.540	0.959	(.69,1.32)	0.800	0.964	(.65,1.41)	0.851	1.070	(.59,1.92)	0.820
Class 3: Social	1.329	(1.04,1.70)	0.024*	1.254	(.97,1.62)	0.080	1.166	(.85,1.60)	0.341	1.267	(.82,1.95)	0.281
Class 4: Least Active	1.663	(1.29,2.14)	<.001***	1.551	(1.19,2.01)	0.001**	1.494	(1.08,2.08)	0.017*	1.040	(.67,1.61)	0.862
Age				1.214	(1.15,1.29)	<.001***	1.205	(1.12,1.29)	<.001***	1.173	(1.06,1.30)	0.002**
Age >80				0.924	(.83,1.03)	0.158	0.922	(.80,1.06)	0.259	0.892	(.74,1.07)	0.224
Age >85				0.848	(.70,1.03)	0.093	0.816	(.62,1.07)	0.137	1.063	(.81,1.39)	0.661
Age >90				1.515	(.99,2.31)	0.054	1.878	(1.03,3.42)	0.040*	0.902	(.50,1.61)	0.729
Sex (male)				0.825	(.69,.99)	0.037*	0.823	(.66,1.03)	0.092	0.874	(.64,1.19)	0.400
Race (non-white)				1.500	(1.04,2.16)	0.030*	1.090	(.59,2.01)	0.783	0.940	(.58,1.52)	0.800
Education (ref: <=HS)												
Some college				0.927	(.74,1.17)	0.522	0.947	(.70,1.28)	0.720	0.650	(.44,.95)	0.028*
College graduate				0.970	(.74,1.28)	0.827	1.028	(.73,1.44)	0.872	1.083	(.66,1.79)	0.755
Professional/Graduate Degree				1.200	(.95,1.52)	0.131	1.206	(.89,1.64)	0.230	0.764	(.52,1.13)	0.174
Study Site (ref: Wake Forest)												
UC Davis				0.895	(.71,1.13)	0.358	1.023	(.75,1.40)	0.885	1.149	(.79,1.67)	0.469
Johns Hopkins				1.073	(.82,1.41)	0.610	1.205	(.85,1.71)	0.299	1.176	(.76,1.83)	0.473
Pittsburgh				0.682	(.53,.88)	0.003**	0.750	(.54,1.04)	0.088	0.737	(.50,1.09)	0.126
Treatment group				1.103	(.93,1.31)	0.267	1.032	(.83,1.28)	0.778	1.106	(.83,1.48)	0.497
Medical comorbidities				1.108	(1.02,1.20)	0.010*	1.166	(1.06,1.29)	0.002**	1.015	(.89,1.16)	0.829
Depressive symptoms (CES-D>=10)				1.782	(1.35,2.35)	<.001***	1.957	(1.37,2.79)	<.001***	0.990	(.63,1.55)	0.963
Model AUC			0.684			0.742						

Note: $p<.05$*, $p<.01$**, $p<.001$***. MCI = Mild Cognitive Impairment, HS = high school. Model 1 is unadjusted for covariates. Model 2 is adjusted for demographic and health covariates. Model 3 is stratified by MCI status.

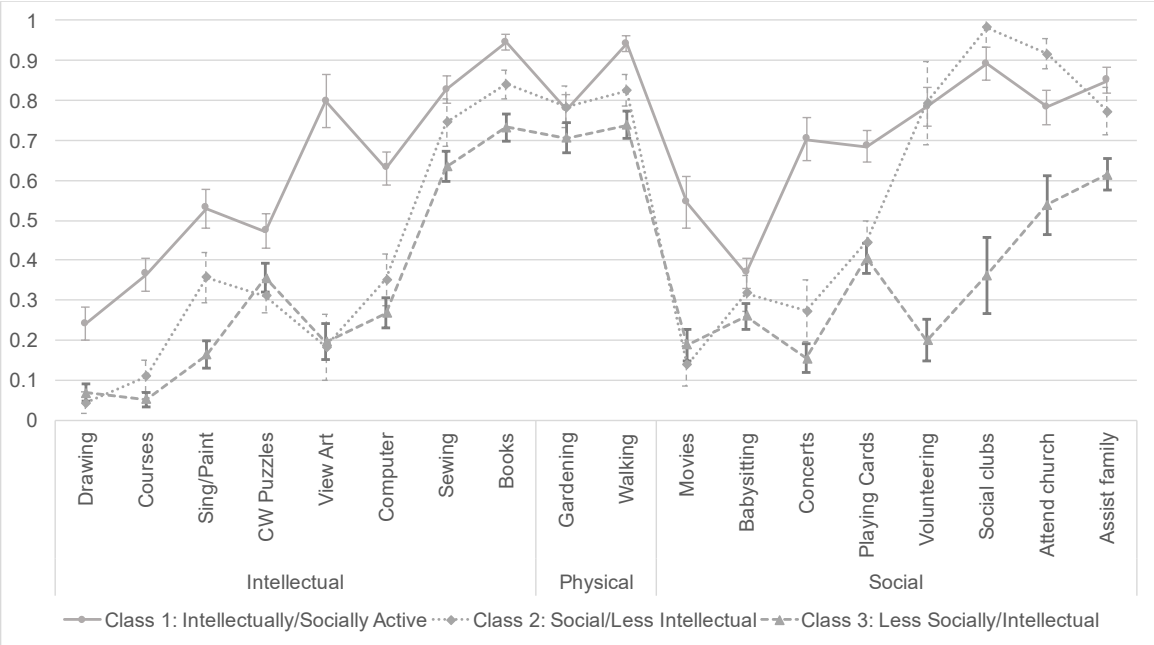
Figure 4.1: Probabilities of engagement in each activity by latent class for the 4-class model



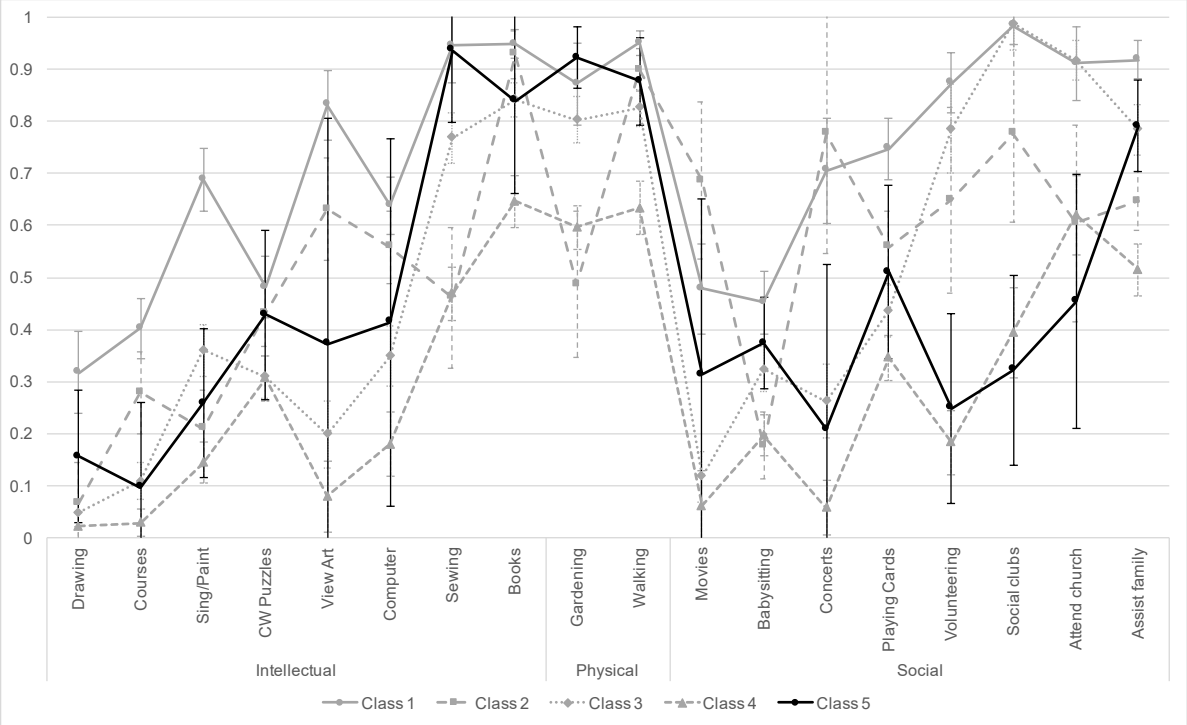
Note. CW = crossword. Error bars represent 95% confidence intervals for item-response probability estimates.

Figure 4.2: Probabilities of engagement in each activity by latent class for the 3- and 5-class models

A. 3-Class Model

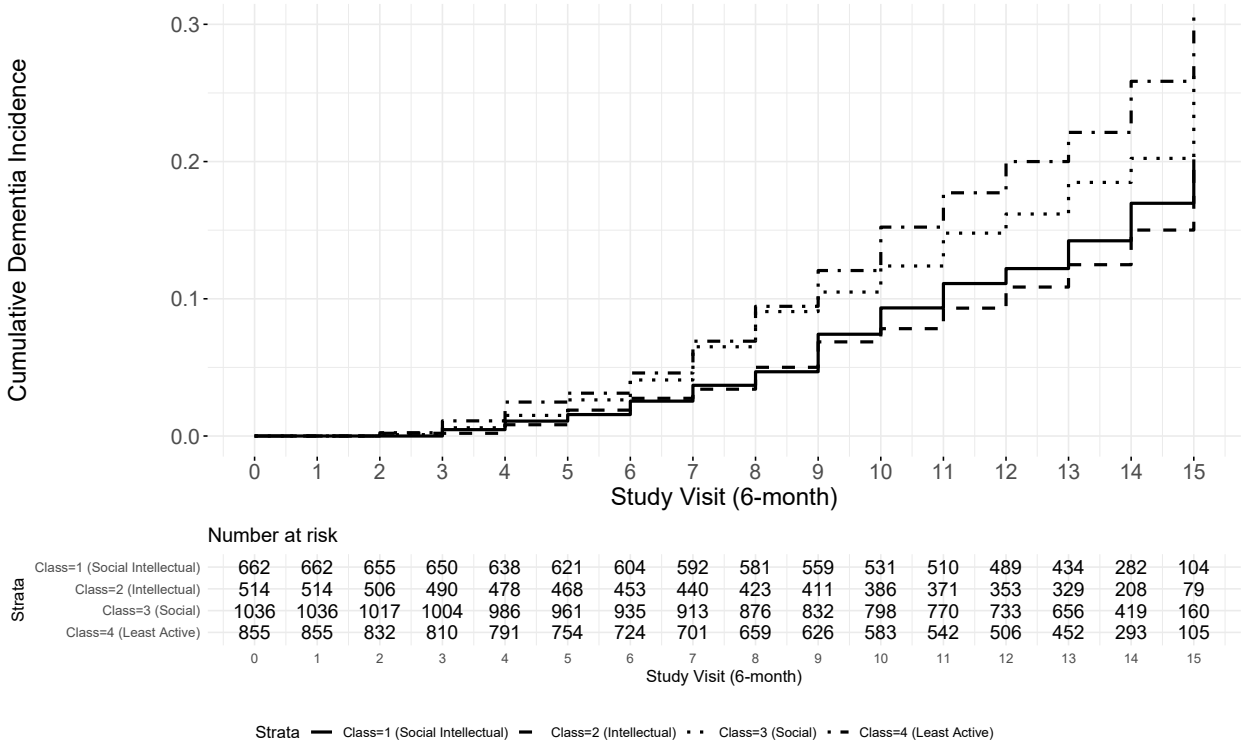


B. 5-Class Model



Note. CW = crossword. Error bars represent 95% confidence intervals for item-response probability estimates.

Figure 4.3: Cumulative incidence curves of time to dementia onset stratified by lifestyle engagement class



Note. Study entry (visit 0) was at date of baseline session. Visits occurred at approximately 6-month intervals.

Supplemental Table 4.1: Unadjusted and adjusted discrete-time proportional hazards models for lifestyle engagement classes predicting time to dementia diagnosis using the Vermunt (2010) approach

	Model 1 (Unadjusted)			Model 2 (Adjusted)			Model 3 (stratified by MCI)					
							Non-MCI (n=2,587)			MCI (n=481)		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Lifestyle engagement group (Ref: Class 1: Social Intellectual)												
Class 2: Intellectual	0.787	(0.47, 1.33)	0.370	0.858	(0.50, 1.47)	0.579	0.888	(0.47, 1.66)	0.709	1.073	(0.33, 3.44)	0.907
Class 3: Social	1.401	(0.98, 2.01)	0.066	1.383	(0.94, 2.03)	0.097	1.250	(0.77, 2.02)	0.360	1.476	(0.75, 2.90)	0.261
Class 4: Least Active	1.822	(1.33, 2.50)	<.001***	1.733	(1.23, 2.44)	0.002**	1.644	(1.07, 2.53)	0.024*	1.141	(0.64, 2.04)	0.656

Note: $p<.05$*, $p<.01$**, $p<.001$***

Model 1 is unadjusted for covariates. Model 2 is adjusted for demographic (age, race, education category, treatment group, study site) and health covariates (medical comorbidities and depressive symptoms). Model 3 is stratified by MCI status.

Supplemental Table 4.2: Unadjusted and adjusted discrete-time proportional hazards models excluding those with extreme propensity scores

	Model 1 (Unadjusted)			Model 2 (Adjusted)			Model 3 (stratified by MCI)					
							Non-MCI (n=2,587)			MCI (n=481)		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Lifestyle engagement group (Ref: Class 1: Social Intellectual)												
Class 2: Intellectual	0.903	(.66,1.24)	0.534	0.958	(.69,1.32)	0.796	0.973	(.66,1.44)	0.891	1.068	(.60,1.91)	0.826
Class 3: Social	1.314	(1.02,1.69)	0.032*	1.233	(.95,1.59)	0.109	1.149	(.83,1.59)	0.397	1.244	(.81,1.91)	0.321
Class 4: Least Active	1.653	(1.28,2.13)	<.001***	1.553	(1.19,2.02)	0.001**	1.518	(1.09,2.12)	0.014*	1.046	(.67,1.62)	0.840

Note: $p<.05$*, $p<.01$**, $p<.001$***

Model 1 is unadjusted for covariates. Model 2 is adjusted for demographic (age, race, education category, treatment group, study site) and health covariates (medical comorbidities and depressive symptoms). Model 3 is stratified by MCI status.

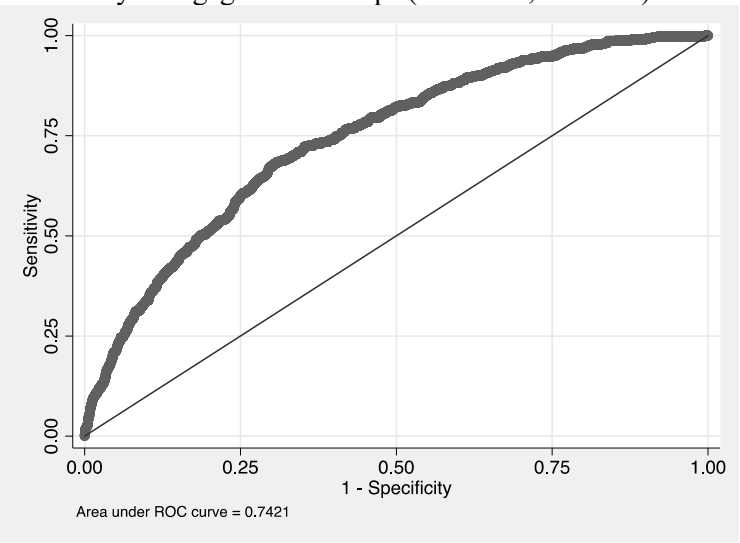
Supplemental Table 4.3: Frequency of Best Fitting Models by Bayesian Information Criterion and Bootstrapped Likelihood Ratio Tests for Ten Semi-Random Subsets of Activities

Classes Enumerated	BIC	BLRT
2-class	0	0
3-class	5	0
4-class	4	3
5-class	1	7
>=6-class	0	0

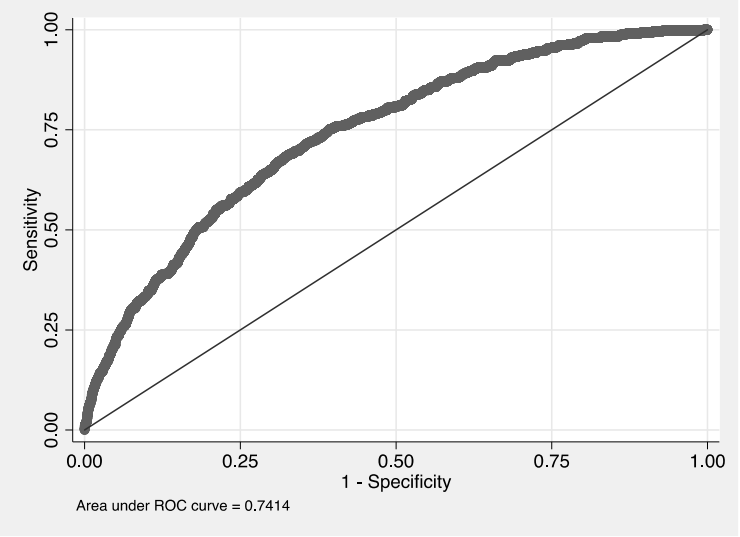
Note. For models where convergence was not achieved or that had more than 3 parameters assigned to extreme boundary values, the *n-1* class model was chosen as the best fitting model for that criteria. BIC = Bayesian Information Criteria, BLRT = Bootstrapped Likelihood Ratio Test.

Supplemental Figure 4.1: Receiver Operating Characteristic curves for the adjusted models of activity variety and lifestyle engagement groups

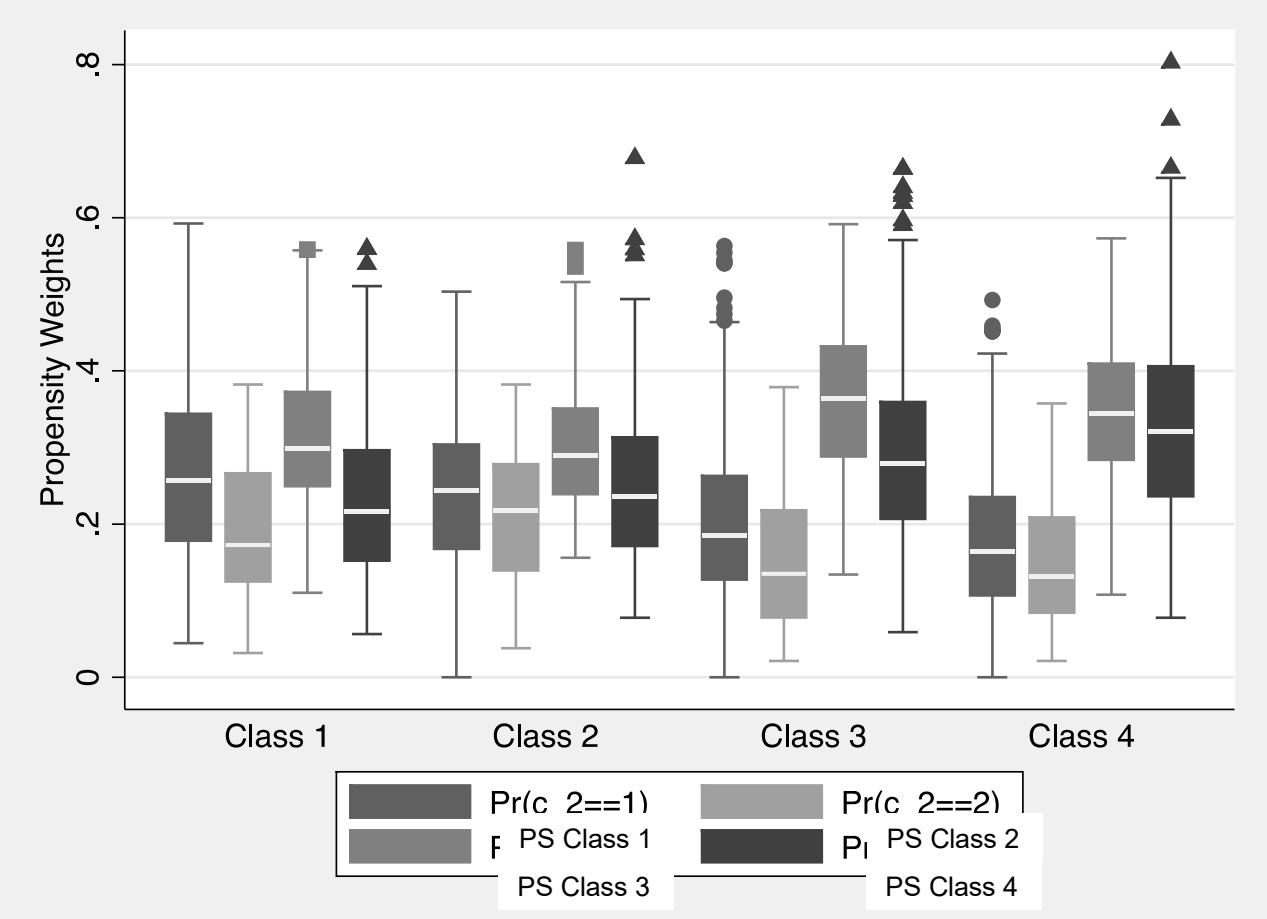
A. Lifestyle Engagement Groups (Table 4.5, Model 2)



B. Activity Variety Count (Table 4.4, Model 2)



Supplemental Figure 4.2: Boxplots of propensity scores stratified by assigned lifestyle engagement group



Note. PS = propensity score
Propensity scores generated using multinomial logistic regression of modal class assignment on baseline age (modeled flexibly using 5-year splines, i.e., >80, >85, >90), sex, race, education, study site, treatment group (intervention vs. control), number of comorbidities, significant depressive symptoms (CES-D>=10). MCI status was not included as a covariate. Differences in range of propensity scores across classes suggest differences in covariate coverage.

Table 5.1: Sample characteristics (N=3,068)

	N (or M)	% (or SD)	Range	
Study Site				
Wake Forest	732	23.85		
UC Davis	914	29.78		
Johns Hopkins	456	14.86		
Pittsburgh	966	31.48		
Age	78.5	3.3	72	96
Sex (male)	1,649	53.73		
Race (white)	2,929	95.44		
Education				
<=HS	1,103	35.95		
some college	775	25.26		
college grad	480	15.65		
professional/grad	710	23.14		
Mild Cognitive Impairment	481	15.68		
Significant Depressive Symptoms (CES-D≥10)	215	7.01		
Self-rated Health				
Fair/Poor	210	6.84		
Good	1,315	42.85		
Very Good	1,237	40.31		
Excellent	291	9.48		
Medical Comorbidities	1.4	1.1	0	7
Lifestyle Engagement Group				
Class 1 (Social Intellectual)	662	21.58		
Class 2 (Intellectual)	514	16.75		
Class 3 (Social)	1,036	33.77		
Class 4 (Least Active)	856	27.90		

Table 5.2: Baseline and longitudinal differences in global cognition by activity class

Global Cognition (z-score)	Model 1 (Unadjusted)			Model 2 (Adjusted)		
	B	SE	p-value	B	SE	p-value
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	0.070	0.057	0.225	-0.006	0.051	0.913
Class 3: Social	-0.394	0.049	<.001***	-0.210	0.044	<.001***
Class 4: Least Active	-0.474	0.051	<.001***	-0.281	0.046	<.001***
Time (years)	-0.055	0.005	<.001***	0.075	0.010	<.001***
Class 2 X Time (years)	-0.017	0.008	0.045*	-0.011	0.008	0.184
Class 3 X Time (years)	-0.007	0.007	0.295	-0.006	0.007	0.364
Class 4 X Time (years)	-0.025	0.008	0.001**	-0.019	0.008	0.012*
AIC	23492			22665		
BIC	23580			22879		

Note: N=3,068; p<.05*, p<.01**, p<.001***

Class 1 = High Intellectual/Social activity, Class 2 = High Social/Less Intellectual activity, Class 3 = Less Intellectual/Social activity, SE = standard error

Beta coefficients for class indicators (e.g., "Class 2: Social") represent standard deviation differences in global cognitive performance at baseline (reference: Class 1).

Beta coefficients for class by time interactions (e.g., "Class 2 X Time") represent differences in annual standard deviation change from baseline in global cognitive performance (reference: Class 1).

Model 1 is unadjusted for covariates. Model 2 is adjusted for treatment group, age, age by time interaction, sex, sex by time interaction, study site, study site by time interaction, race, education, significant depressive symptoms (CES-D≥10), and number of medical comorbidities.

Table 5.3. Baseline and longitudinal differences in domain-specific cognitive performance by activity class

	Model 1 (Unadjusted)			Model 2 (Adjusted)		
Cognitive Domain (z-scores)	B	SE	p-value	B	SE	p-value
Memory						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	-0.024	0.058	0.679	-0.051	0.054	0.346
Class 3: Social	-0.277	0.049	<.001***	-0.146	0.047	0.002**
Class 4: Least Active	-0.392	0.051	<.001***	-0.252	0.049	<.001***
Time (years)	-0.013	0.007	0.069	0.123	0.012	<.001***
Class 2 X Time (years)	-0.020	0.011	0.056	-0.017	0.010	0.095
Class 3 X Time (years)	-0.013	0.009	0.161	-0.010	0.009	0.246
Class 4 X Time (years)	-0.026	0.010	0.007**	-0.020	0.009	0.035*
AIC	28726			28221		
BIC	28815			28436		
Executive Functioning						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	0.054	0.057	0.341	0.047	0.055	0.396
Class 3: Social	-0.337	0.048	<.001***	-0.189	0.047	<.001***
Class 4: Least Active	-0.434	0.050	<.001***	-0.240	0.050	<.001***
Time (years)	-0.078	0.006	<.001***	-0.009	0.010	0.337
Class 2 X Time (years)	-0.001	0.009	0.936	0.003	0.009	0.748
Class 3 X Time (years)	0.006	0.007	0.381	0.006	0.007	0.379
Class 4 X Time (years)	-0.002	0.008	0.799	-0.001	0.008	0.852
AIC	27601			27341		
BIC	27690			27555		
Attention						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	0.104	0.057	0.068	0.076	0.055	0.169
Class 3: Social	-0.205	0.048	<.001***	-0.093	0.047	0.049*
Class 4: Least Active	-0.283	0.050	<.001***	-0.143	0.050	0.004**
Time (years)	-0.043	0.006	<.001***	0.030	0.011	0.004**
Class 2 X Time (years)	-0.007	0.009	0.431	-0.008	0.009	0.363
Class 3 X Time (years)	-0.012	0.008	0.118	-0.010	0.008	0.212
Class 4 X Time (years)	-0.022	0.008	0.008**	-0.019	0.008	0.023*
AIC	28613			28345		
BIC	28702			28559		
Language						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	0.020	0.057	0.728	-0.034	0.053	0.522
Class 3: Social	-0.315	0.048	<.001***	-0.186	0.045	<.001***
Class 4: Least Active	-0.299	0.050	<.001***	-0.174	0.048	<.001***
Time (years)	-0.029	0.006	<.001***	0.053	0.010	<.001***
Class 2 X Time (years)	-0.002	0.009	0.785	-0.004	0.008	0.658
Class 3 X Time (years)	0.009	0.007	0.202	0.010	0.007	0.171
Class 4 X Time (years)	-0.003	0.008	0.718	-0.003	0.008	0.741
AIC	26380			25780		
BIC	26468			25994		
Construction						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	0.087	0.059	0.141	-0.052	0.051	0.309

Class 3: Social	-0.230	0.050	<.001***	-0.110	0.044	0.012*
Class 4: Least Active	-0.230	0.052	<.001***	-0.152	0.046	0.001**
Time (years)	0.002	0.006	0.695	0.133	0.010	<.001***
Class 2 X Time (years)	-0.034	0.009	<.001***	-0.021	0.009	0.021*
Class 3 X Time (years)	-0.010	0.008	0.216	-0.008	0.008	0.282
Class 4 X Time (years)	-0.024	0.008	0.004**	-0.015	0.008	0.063
AIC	28649			27647		
BIC	28737			27862		

Note: n=3,068; p<.05*, p<.01**, p<.001***

SE = standard error

Beta coefficients for class indicators (e.g., "Class 2: Social") represent standard deviation differences in domain-specific cognitive performance at baseline (reference: Class 1).

Beta coefficients for class by time interactions (e.g., "Class 2 X Time") represent differences in annual standard deviation change from baseline in domain-specific cognitive performance (reference: Class 1).

Model 1 is unadjusted for covariates. Model 2 is adjusted for treatment group, age, age by time interaction, sex, sex by time interaction, study site, study site by time interaction, race, education, significant depressive symptoms (CES-D≥10), and number of medical comorbidities.

Supplemental Table 5.1: Baseline and longitudinal differences in global cognitive performance by activity class with spline terms

	Model A (Original)			Model B (Year 3 Spline)			Model C (Age Splines)			Model D (All Splines)		
Global Cognition (z-scores)	B	SE	p-value	B	SE	p-value	B	SE	p-value	B	SE	p-value
(ref: Class 1: Social Intellectual)												
Class 2: Intellectual	-0.005	0.050	0.919	-0.018	0.051	0.731	-0.011	0.051	0.828	-0.020	0.051	0.698
Class 3: Social	-0.211	0.043	<.001***	-0.217	0.044	<.001***	-0.218	0.044	<.001***	-0.218	0.044	<.001***
Class 4: Least Active	-0.281	0.046	<.001***	-0.301	0.047	<.001***	-0.283	0.046	<.001***	-0.303	0.047	<.001***
Annual Change (no spline)												
Class 2 X Time (years)	-0.011	0.008	0.183				-0.010	0.008	0.207			
Class 3 X Time (years)	-0.006	0.007	0.424				-0.004	0.007	0.604			
Class 4 X Time (years)	-0.019	0.007	0.012				-0.018	0.007	0.018			
Annual Change (spline)												
< 3 years												
Class 2 X Time (years)				0.003	0.014	0.828				0.003	0.014	0.808
Class 3 X Time (years)				0.001	0.012	0.941				0.001	0.012	0.913
Class 4 X Time (years)				0.004	0.012	0.727				0.004	0.012	0.723
>= 3 years												
Class 2 X Time (years)				-0.024	0.014	0.090				-0.024	0.014	0.094
Class 3 X Time (years)				-0.005	0.012	0.657				-0.005	0.012	0.703
Class 4 X Time (years)				-0.035	0.013	0.007				-0.036	0.013	0.005
AIC	22503			22402			22467			22399		
BIC	22718			22646			22726			22687		
LR Test	Chi	df	p-value									
A vs. B	109.51	4	<.001									
A vs. C	47.88	6	<.001									
B vs. D	14.63	6	0.023									

Note. n=3,068; p<.05*, p<.01**, p<.001***, SE = standard error

Beta coefficients for class indicators (e.g., "Class 2: Social") represent standard deviation differences in cognitive performance at baseline (reference: Class 1). Beta coefficients for class by time interactions (e.g., "Class 2 X Time") represent differences in annual standard deviation change from baseline cognitive performance (reference: Class 1). All models used Maximum Likelihood estimation to allow for likelihood ratio tests (estimates in Model A will differ slightly from Model 2 in Table 1). Model A is the original fully adjusted model (Table 1, Model 2). Model B further adjusts for a spline term at year 3, and the year 3 spline by class interaction (4 additional parameters). Model C has additional spline terms for each 5-year age interval (i.e., 80, 85, 90) and their interactions with time (6 additional parameters).

Supplemental Table 5.2: Baseline and longitudinal differences in memory performance by activity class with spline terms

	Model A (Original)			Model B (Year 3 Spline)			Model C (Age Splines)			Model D (All Splines)		
Memory (z-scores)	B	SE	p-value	B	SE	p-value	B	SE	p-value	B	SE	p-value
(ref: Class 1: Social Intellectual)												
Class 2: Intellectual	-0.051	0.054	0.345	-0.059	0.055	0.287	-0.057	0.054	0.294	-0.062	0.055	0.261
Class 3: Social	-0.146	0.047	0.002	-0.147	0.048	0.002	-0.152	0.047	0.001	-0.149	0.048	0.002
Class 4: Least Active	-0.252	0.049	<.001	-0.274	0.050	<.001	-0.255	0.049	<.001	-0.275	0.050	<.001
Annual Change (no spline)												
Class 2 X Time (years)	-0.017	0.010	0.094				-0.017	0.010	0.105			
Class 3 X Time (years)	-0.010	0.009	0.246				-0.008	0.009	0.329			
Class 4 X Time (years)	-0.020	0.009	0.035				-0.019	0.009	0.039			
Annual Change (spline)												
< 3 years												
Class 2 X Time (years)				-0.009	0.019	0.632				-0.009	0.019	0.630
Class 3 X Time (years)				-0.011	0.016	0.493				-0.011	0.016	0.491
Class 4 X Time (years)				0.007	0.017	0.676				0.007	0.017	0.690
>= 3 years												
Class 2 X Time (years)				-0.025	0.019	0.186				-0.024	0.019	0.201
Class 3 X Time (years)				-0.006	0.016	0.724				-0.004	0.016	0.802
Class 4 X Time (years)				-0.044	0.017	0.012				-0.045	0.017	0.010
AIC	28065			28047			28051			28043		
BIC	28279			28291			28310			28331		
LR Test	Chi	df	p-value									
A vs. B	25.61	4	<.001									
A vs. C	25.98	6	<.001									
B vs. D	16.42	6	0.012									

Note. n=3,068; p<.05*, p<.01**, p<.001***, SE = standard error. All models used Maximum Likelihood estimation to allow for likelihood ratio tests (estimates in Model A will differ slightly from Model 2 in Table 1). Model A is the original fully adjusted model (Table 1, Model 2). Model B further adjusts for a spline term at year 3, and the year 3 spline by class interaction (4 additional parameters). Model C has additional spline terms for each 5-year age interval (i.e., 80, 85, 90) and their interactions with time (6 additional parameters).

Supplemental Table 5.3: Baseline and longitudinal differences in executive functioning by activity class with spline terms

Executive Functioning (z-scores)	Model A (Original) B	SE	p-value	Model B (Year 3 Spline) B	SE	p-value	Model C (Age Splines) B	SE	p-value	Model D (All Splines) B	SE	p-value
(ref: Class 1: Social Intellectual)												
Class 2: Intellectual	0.047	0.055	0.395	0.036	0.056	0.523	0.045	0.055	0.413	0.037	0.056	0.504
Class 3: Social	-0.189	0.047	<.001	-0.187	0.048	<.001	-0.191	0.047	<.001	-0.185	0.048	<.001
Class 4: Least Active	-0.240	0.050	<.001	-0.242	0.051	<.001	-0.241	0.050	<.001	-0.243	0.051	<.001
Annual Change (no spline)												
Class 2 X Time (years)	0.003	0.009	0.748				0.003	0.009	0.744			
Class 3 X Time (years)	0.006	0.007	0.377				0.007	0.007	0.334			
Class 4 X Time (years)	-0.001	0.008	0.852				-0.001	0.008	0.849			
Annual Change (spline)												
< 3 years												
Class 2 X Time (years)				0.015	0.018	0.402				0.014	0.018	0.429
Class 3 X Time (years)				0.000	0.015	0.988				0.000	0.015	0.981
Class 4 X Time (years)				-0.008	0.016	0.629				-0.007	0.016	0.644
>= 3 years												
Class 2 X Time (years)				-0.009	0.018	0.627				-0.008	0.018	0.649
Class 3 X Time (years)				0.017	0.015	0.270				0.017	0.015	0.266
Class 4 X Time (years)				0.010	0.016	0.532				0.008	0.016	0.607
AIC	27179			27150			27180			27150		
BIC	27394			27394			27439			27438		
LR Test	Chi	df	p-value									
A vs. B	37.12	4	<.001									
A vs. C	11.41	6	0.077									
B vs. D	12.42	6	0.053									

Note. n=3,068; p<.05*, p<.01**, p<.001***, SE = standard error. All models used Maximum Likelihood estimation to allow for likelihood ratio tests (estimates in Model A will differ slightly from Model 2 in Table 1). Model A is the original fully adjusted model (Table 1, Model 2). Model B further adjusts for a spline term at year 3, and the year 3 spline by class interaction (4 additional parameters). Model C has additional spline terms for each 5-year age interval (i.e., 80, 85, 90) and their interactions with time (6 additional parameters).

Supplemental Table 5.4: Baseline and longitudinal differences in language by activity class with spline terms

	Model A (Original)			Model B (Year 3 Spline)			Model C (Age Splines)			Model D (All Splines)		
Language (z-scores)	B	SE	p-value	B	SE	p-value	B	SE	p-value	B	SE	p-value
(ref: Class 1: Social Intellectual)												
Class 2: Intellectual	-0.034	0.053	0.521	-0.046	0.054	0.391	-0.038	0.053	0.471	-0.049	0.054	0.366
Class 3: Social	-0.186	0.045	<.001	-0.202	0.046	<.001	-0.192	0.045	<.001	-0.204	0.046	<.001
Class 4: Least Active	-0.174	0.048	<.001	-0.196	0.049	<.001	-0.176	0.048	<.001	-0.197	0.049	<.001
Annual Change (no spline)												
Class 2 X Time (years)	-0.004	0.008	0.657				-0.003	0.008	0.702			
Class 3 X Time (years)	0.010	0.007	0.170				0.011	0.007	0.127			
Class 4 X Time (years)	-0.003	0.008	0.741				-0.002	0.008	0.837			
Annual Change (spline)												
< 3 years												
Class 2 X Time (years)				0.010	0.017	0.531				0.011	0.017	0.498
Class 3 X Time (years)				0.026	0.014	0.057				0.027	0.014	0.050
Class 4 X Time (years)				0.022	0.015	0.133				0.022	0.015	0.131
>= 3 years												
Class 2 X Time (years)				-0.017	0.017	0.305				-0.017	0.017	0.300
Class 3 X Time (years)				-0.004	0.014	0.768				-0.004	0.014	0.764
Class 4 X Time (years)				-0.024	0.015	0.116				-0.024	0.015	0.114
AIC	25618			25599			25616			25607		
BIC	25832			25843			25875			25895		
LR Test	Chi	df	p-value									
A vs. B	26.75	4	<.001									
A vs. C	13.81	6	0.032									
B vs. D	3.91	6	0.689									

Note. n=3,068; p<.05*, p<.01**, p<.001***, SE = standard error. All models used Maximum Likelihood estimation to allow for likelihood ratio tests (estimates in Model A will differ slightly from Model 2 in Table 1). Model A is the original fully adjusted model (Table 1, Model 2). Model B further adjusts for a spline term at year 3, and the year 3 spline by class interaction (4 additional parameters). Model C has additional spline terms for each 5-year age interval (i.e., 80, 85, 90) and their interactions with time (6 additional parameters).

Supplemental Table 5.5: Baseline and longitudinal differences in attention by activity class with spline terms

	Model A (Original)			Model B (Year 3 Spline)			Model C (Age Splines)			Model D (All Splines)		
Attention (z-scores)	B	SE	p-value	B	SE	p-value	B	SE	p-value	B	SE	p-value
(ref: Class 1: Social Intellectual)												
Class 2: Intellectual	0.076	0.055	0.168	0.073	0.056	0.193	0.070	0.055	0.204	0.070	0.056	0.211
Class 3: Social	-0.093	0.047	0.049	-0.097	0.048	0.045	-0.100	0.047	0.034	-0.099	0.048	0.041
Class 4: Least Active	-0.143	0.050	0.004	-0.156	0.051	0.002	-0.147	0.050	0.003	-0.158	0.051	0.002
Annual Change (no spline)												
Class 2 X Time (years)	-0.008	0.009	0.360				-0.008	0.009	0.394			
Class 3 X Time (years)	-0.010	0.008	0.212				-0.008	0.008	0.285			
Class 4 X Time (years)	-0.019	0.008	0.023				-0.017	0.008	0.036			
Annual Change (spline)												
< 3 years												
Class 2 X Time (years)				-0.009	0.019	0.645				-0.008	0.019	0.677
Class 3 X Time (years)				-0.010	0.016	0.543				-0.009	0.016	0.573
Class 4 X Time (years)				-0.010	0.017	0.554				-0.010	0.017	0.549
>= 3 years												
Class 2 X Time (years)				-0.007	0.019	0.716				-0.007	0.019	0.705
Class 3 X Time (years)				-0.005	0.016	0.758				-0.005	0.016	0.765
Class 4 X Time (years)				-0.022	0.017	0.207				-0.021	0.017	0.222
AIC	28185			28142			28177			28043		
BIC	28400			28386			28436			28331		
LR Test	Chi	df	p-value									
A vs. B	51.28	4	<.001									
A vs. C	20.19	6	0.003									
B vs. D	4.71	6	0.582									

Note. n=3,068; p<.05*, p<.01**, p<.001***, SE = standard error. All models used Maximum Likelihood estimation to allow for likelihood ratio tests (estimates in Model A will differ slightly from Model 2 in Table 1). Model A is the original fully adjusted model (Table 1, Model 2). Model B further adjusts for a spline term at year 3, and the year 3 spline by class interaction (4 additional parameters). Model C has additional spline terms for each 5-year age interval (i.e., 80, 85, 90) and their interactions with time (6 additional parameters).

Supplemental Table 5.6: Baseline and longitudinal differences in visuospatial construction by activity class with spline terms

	Model A (Original)			Model B (Year 3 Spline)			Model C (Age Splines)			Model D (All Splines)		
Construction (z-scores)	B	SE	p-value	B	SE	p-value	B	SE	p-value	B	SE	p-value
(ref: Class 1: Social Intellectual)												
Class 2: Intellectual	-0.052	0.051	0.307	-0.065	0.052	0.214	-0.055	0.051	0.278	-0.065	0.052	0.214
Class 3: Social	-0.110	0.043	0.011	-0.118	0.045	0.008	-0.114	0.044	0.009	-0.117	0.045	0.009
Class 4: Least Active	-0.152	0.046	0.001	-0.172	0.047	<.001	-0.154	0.046	0.001	-0.172	0.047	<.001
Annual Change (no spline)												
Class 2 X Time (years)	-0.021	0.009	0.021				-0.020	0.009	0.024			
Class 3 X Time (years)	-0.008	0.008	0.282				-0.007	0.008	0.346			
Class 4 X Time (years)	-0.015	0.008	0.063				-0.015	0.008	0.068			
Annual Change (spline)												
< 3 years												
Class 2 X Time (years)				-0.007	0.019	0.723				-0.007	0.019	0.722
Class 3 X Time (years)				-0.003	0.016	0.861				-0.003	0.016	0.852
Class 4 X Time (years)				0.002	0.017	0.886				0.003	0.017	0.868
>= 3 years												
Class 2 X Time (years)				-0.034	0.019	0.076				-0.033	0.019	0.079
Class 3 X Time (years)				-0.009	0.016	0.564				-0.008	0.016	0.593
Class 4 X Time (years)				-0.027	0.017	0.114				-0.029	0.017	0.091
AIC	27484			27448			27478			27449		
BIC	27698			27691			27737			27738		
LR Test	Chi	df	p-value									
A vs. B	44.60	4	<.001									
A vs. C	17.98	6	0.006									
B vs. D	10.12	6	0.120									

Note. n=3,068; p<.05*, p<.01**, p<.001***, SE = standard error. All models used Maximum Likelihood estimation to allow for likelihood ratio tests (estimates in Model A will differ slightly from Model 2 in Table 1). Model A is the original fully adjusted model (Table 1, Model 2). Model B further adjusts for a spline term at year 3, and the year 3 spline by class interaction (4 additional parameters). Model C has additional spline terms for each 5-year age interval (i.e., 80, 85, 90) and their interactions with time (6 additional parameters).

Supplemental Table 5.7. Baseline and longitudinal differences in domain-specific cognitive performance by activity class, excluding individuals with prevalent Mild Cognitive Impairment

	Model 1 (Unadjusted)			Model 2 (Adjusted)		
Cognitive Domain (z-scores)	**B**	**SE**	**p-value**	**B**	**SE**	**p-value**
Global Cognition						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	0.039	0.056	0.487	-0.035	0.049	0.481
Class 3: Social	-0.350	0.048	<.001***	-0.156	0.043	<.001***
Class 4: Least Active	-0.340	0.051	<.001***	-0.163	0.046	<.001***
Time (years)	-0.054	0.006	<.001***	0.067	0.010	<.001***
Class 2 X Time (years)	-0.015	0.009	0.090	-0.008	0.009	0.325
Class 3 X Time (years)	-0.007	0.007	0.344	-0.005	0.007	0.512
Class 4 X Time (years)	-0.031	0.008	<.001***	-0.025	0.008	<.001***
AIC	19885			19223		
BIC	19972			19434		
Memory						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	-0.044	0.057	0.436	-0.072	0.053	0.174
Class 3: Social	-0.237	0.049	<.001***	-0.096	0.047	0.038*
Class 4: Least Active	-0.269	0.052	<.001***	-0.139	0.050	0.005**
Time (years)	-0.013	0.007	0.060	0.116	0.012	<.001***
Class 2 X Time (years)	-0.020	0.011	0.139	-0.013	0.011	0.236
Class 3 X Time (years)	-0.013	0.009	0.285	-0.007	0.009	0.472
Class 4 X Time (years)	-0.026	0.010	0.002**	-0.024	0.010	0.015*
AIC	24643			24222		
BIC	24730			24432		
Executive Functioning						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	0.012	0.058	0.836	0.003	0.056	0.956
Class 3: Social	-0.300	0.050	<.001***	-0.145	0.049	0.003**
Class 4: Least Active	-0.366	0.053	<.001***	-0.183	0.053	<.001***
Time (years)	-0.081	0.006	<.001***	-0.017	0.010	0.106
Class 2 X Time (years)	0.004	0.009	0.673	0.007	0.009	0.436
Class 3 X Time (years)	0.008	0.008	0.286	0.008	0.008	0.303
Class 4 X Time (years)	-0.005	0.008	0.582	-0.004	0.008	0.653
AIC	23866			23669		
BIC	23953			23880		
Attention						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	0.082	0.058	0.154	0.056	0.056	0.315
Class 3: Social	-0.182	0.050	<.001***	-0.066	0.049	0.178

Class 4: Least Active	-0.211	0.053	<.001***	-0.083	0.052	0.115
Time (years)	-0.042	0.006	<.001***	0.027	0.011	0.013*
Class 2 X Time (years)	-0.009	0.009	0.321	-0.011	0.009	0.230
Class 3 X Time (years)	-0.014	0.008	0.078	-0.011	0.008	0.157
Class 4 X Time (years)	-0.030	0.009	<.001***	-0.027	0.009	0.002**
AIC	24644			24448		
BIC	24732			24658		
Language						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	-0.005	0.058	0.930	-0.044	0.054	0.413
Class 3: Social	-0.301	0.050	<.001***	-0.161	0.047	0.001**
Class 4: Least Active	-0.223	0.053	<.001***	-0.102	0.050	0.043*
Time (years)	-0.031	0.006	<.001***	0.045	0.010	<.001***
Class 2 X Time (years)	0.001	0.009	0.947	-0.001	0.009	0.910
Class 3 X Time (years)	0.008	0.008	0.304	0.009	0.007	0.245
Class 4 X Time (years)	-0.007	0.008	0.424	-0.007	0.008	0.419
AIC	22884			22420		
BIC	22971			22631		
Construction						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	0.094	0.059	0.109	-0.057	0.050	0.259
Class 3: Social	-0.187	0.050	<.001***	-0.062	0.044	0.156
Class 4: Least Active	-0.104	0.053	0.051	-0.050	0.047	0.288
Time (years)	0.002	0.006	0.788	0.129	0.010	<.001***
Class 2 X Time (years)	-0.037	0.010	<.001***	-0.022	0.009	0.015*
Class 3 X Time (years)	-0.015	0.008	0.061	-0.014	0.008	0.071
Class 4 X Time (years)	-0.031	0.009	<.001***	-0.021	0.008	0.014*
AIC	24536			27647		
BIC	24624			27862		

Note: n=2,587; p<.05*, p<.01**, p<.001***
SE = standard error

Beta coefficients for class indicators (e.g., "Class 2: Social") represent standard deviation differences in domain-specific cognitive performance at baseline (reference: Class 1).

Beta coefficients for class by time interactions (e.g., "Class 2 X Time") represent differences in annual standard deviation change from baseline in domain-specific cognitive performance (reference: Class 1).

Model 1 is unadjusted for covariates. Model 2 is adjusted for treatment group, age, age by time interaction, sex, sex by time interaction, study site, study site by time interaction, race, education, significant depressive symptoms (CES-D≥10), and number of medical comorbidities.

Table 6.1: Sample characteristics (N=3,068)

	N (or M)	% (or SD)	Range	
Study Site				
Wake Forest	732	23.85		
UC Davis	914	29.78		
Johns Hopkins	456	14.86		
Pittsburgh	966	31.48		
Age	78.5	3.3	72	96
Sex (male)	1,649	53.73		
Race (white)	2,929	95.44		
Education				
<=HS	1,103	35.95		
some college	775	25.26		
college grad	480	15.65		
professional/grad	710	23.14		
Mild Cognitive Impairment	481	15.68		
Significant Depressive Symptoms (CES-D≥10)	215	7.01		
Self-rated Health				
Fair/Poor	210	6.84		
Good	1,315	42.85		
Very Good	1,237	40.31		
Excellent	291	9.48		
Medical Comorbidities	1.4	1.1	0	7
Lifestyle Engagement Group				
Class 1 (Social Intellectual)	662	21.58		
Class 2 (Intellectual)	514	16.75		
Class 3 (Social)	1,036	33.77		
Class 4 (Least Active)	856	27.90		

Table 6.2: Baseline and longitudinal differences in physical frailty criteria by activity class

	Model 1 (Unadjusted)			Model 2 (Adjusted)		
Physical Frailty Criteria	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Slow Gait (>=7 sec)						
Baseline Differences						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	2.91	(1.44, 5.90)	0.003**	2.89	(1.45, 5.74)	0.002**
Class 3: Social	2.72	(1.47, 5.04)	0.002**	2.04	(1.11, 3.74)	0.021*
Class 4: Least Active	7.06	(3.79, 13.13)	<.001***	4.24	(2.30, 7.81)	<.001***
Time (years)	1.74	(1.53, 1.97)	<.001***	1.34	(1.13, 1.6)	0.001**
Longitudinal Differences						
Class 2 X Time (years)	0.87	(0.74, 1.03)	0.097	0.85	(0.73, 1.00)	0.048*
Class 3 X Time (years)	0.93	(0.80, 1.07)	0.291	0.92	(0.80, 1.06)	0.243
Class 4 X Time (years)	0.93	(0.81, 1.08)	0.333	0.93	(0.81, 1.07)	0.315
Exhaustion (Fried et al., 2001)						
Baseline Differences						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	1.22	(0.85, 1.75)	0.279	1.10	(0.79, 1.54)	0.563
Class 3: Social	1.28	(0.94, 1.73)	0.117	1.16	(0.87, 1.54)	0.315
Class 4: Least Active	2.31	(1.7, 3.15)	<.001***	1.85	(1.38, 2.48)	<.001***
Time (years)	1.17	(1.11, 1.23)	<.001***	1.13	(1.04, 1.21)	0.002**
Longitudinal Differences						
Class 2 X Time (years)	0.94	(0.87, 1.02)	0.132	0.96	(0.89, 1.04)	0.326
Class 3 X Time (years)	0.98	(0.92, 1.05)	0.621	0.98	(0.92, 1.05)	0.578
Class 4 X Time (years)	0.93	(0.87, 0.99)	0.027*	0.93	(0.87, 0.99)	0.035*
Exhaustion (Maastricht)						
Baseline Differences						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	1.22	(0.83, 1.82)	0.313	1.20	(0.82, 1.75)	0.345
Class 3: Social	1.38	(0.99, 1.92)	0.06	1.24	(0.90, 1.71)	0.195
Class 4: Least Active	2.13	(1.51, 3.01)	<.001***	1.69	(1.21, 2.37)	0.002**
Time (years)	1.22	(1.15, 1.29)	<.001***	1.14	(1.06, 1.23)	<.001***
Longitudinal Differences						
Class 2 X Time (years)	0.99	(0.91, 1.06)	0.703	0.99	(0.92, 1.07)	0.789
Class 3 X Time (years)	0.95	(0.89, 1.02)	0.151	0.94	(0.88, 1.01)	0.078

Class 4 X Time (years)	0.96	(0.90, 1.03)	0.236	0.95	(0.89, 1.02)	0.140
Weakness						
Baseline Differences						
(ref: Class 1: Social Intellectual)						
Class 2: Intellectual	0.92	(0.59, 1.42)	0.699	1.08	(0.70, 1.66)	0.718
Class 3: Social	0.81	(0.56, 1.17)	0.271	0.90	(0.63, 1.31)	0.591
Class 4: Least Active	0.74	(0.50, 1.08)	0.121	0.86	(0.58, 1.28)	0.456
Time (years)	1.00	(0.91, 1.10)	0.958	0.92	(0.80, 1.05)	0.215
Longitudinal Differences						
Class 2 X Time (years)	0.95	(0.83, 1.09)	0.485	0.94	(0.82, 1.08)	0.359
Class 3 X Time (years)	1.07	(0.96, 1.20)	0.223	1.07	(0.96, 1.21)	0.226
Class 4 X Time (years)	1.09	(0.96, 1.23)	0.179	1.07	(0.94, 1.21)	0.307

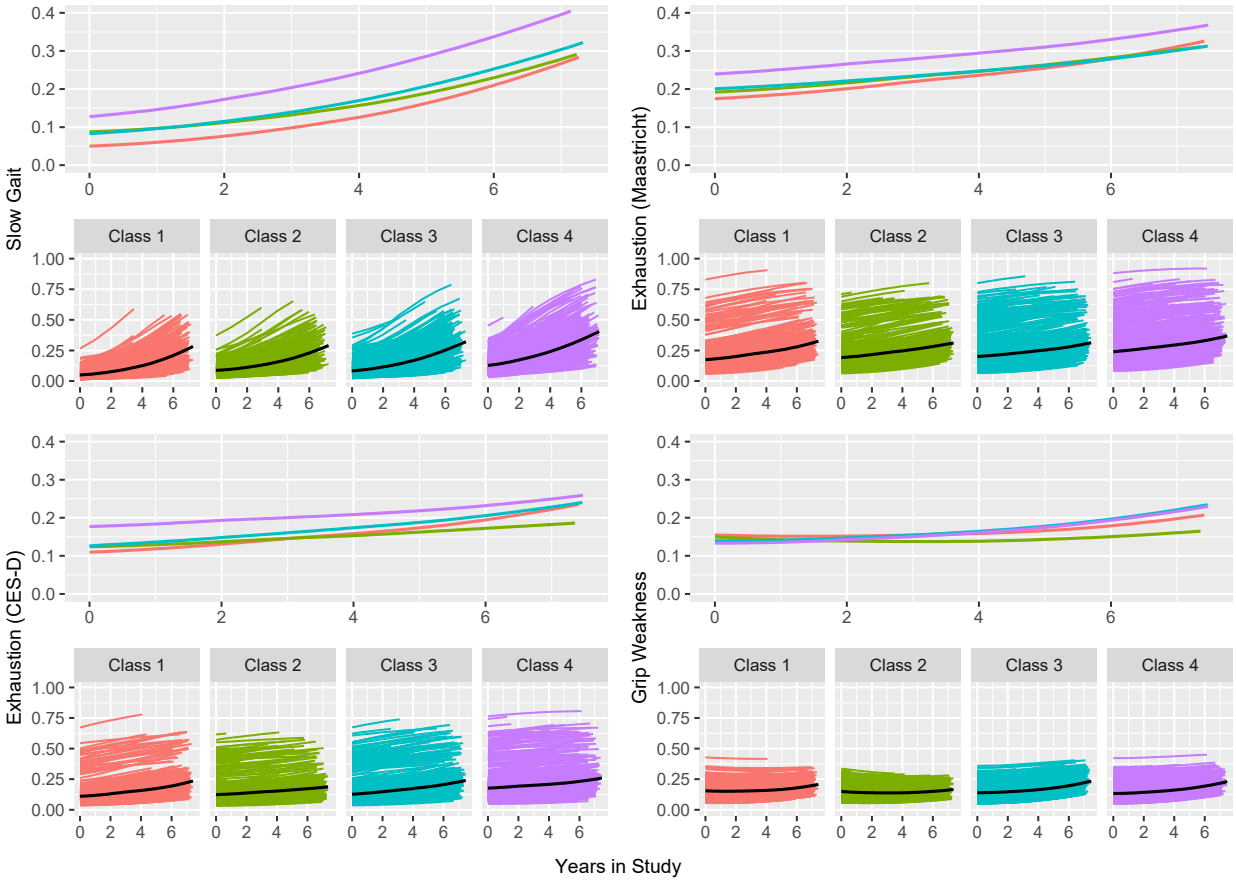
Note: n=3,068; $p<.05$*, $p<.01$**, $p<.001$***

Odds ratios for class indicators (e.g., "Class 2") represent difference in odds of the frailty symptom between that class and Class 1 at baseline for an "average" participant (random intercept is 0).

Odds ratios for class by time indicators (e.g., "Class 2 X Time (years)") represent change in odds ratios of the frailty symptom between that class and Class 1 per year in study for an "average" participant (random intercept and slope is 0).

Model 1 is unadjusted for covariates. Model 2 is adjusted for age, age by time interaction, sex, sex by time interaction, study site, study site by time interaction, race, education, treatment group, significant depressive symptoms (CES-D≥10), and number of medical comorbidities.

Figure 6.1: Average and subject-specific marginal predicted probabilities of frailty criteria across lifestyle engagement classes



Note. The top plots for each symptom are of average marginal predicted probabilities by class. The bottom plots are of average and subject-specific marginal predicted probabilities indicated by thick and thin lines, respectively, stratified by class.

Red = Social Intellectual (Class 1), green = Intellectual (Class 2), teal = Social (Class 3), purple = Least Active (Class 4).

Supplemental Table 6.1: Baseline and longitudinal differences in physical frailty criteria by activity class for the 3-class model

	Model 1 (Unadjusted)			Model 2 (Adjusted)		
Physical Frailty Criteria	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Slow Gait (>=7 sec)						
Baseline Differences (ref: Class 1)						
Class 2	2.08	(1.23, 3.52)	0.006**	1.55	(0.92, 2.61)	0.097
Class 3	5.67	(3.42, 9.38)	<.001***	3.60	(2.19, 5.90)	<.001***
Time (years)	1.68	(1.52, 1.86)	<.001***	1.30	(1.10, 1.52)	0.002**
Longitudinal Differences						
Class 2 X Time (years)	0.95	(0.84, 1.07)	0.384	0.95	(0.84, 1.07)	0.380
Class 3 X Time (years)	0.94	(0.84, 1.06)	0.325	0.95	(0.84, 1.06)	0.351
Exhaustion (CES-D)						
Baseline Differences (ref: Class 1)						
Class 2	1.34	(1.02, 1.76)	0.034*	1.26	(0.97, 1.63)	0.077
Class 3	2.41	(1.85, 3.14)	<.001***	2.03	(1.58, 2.61)	<.001***
Time (years)	1.16	(1.11, 1.21)	<.001***	1.13	(1.05, 1.21)	0.001**
Longitudinal Differences						
Class 2 X Time (years)	0.99	(0.93, 1.05)	0.679	0.98	(0.92, 1.04)	0.494
Class 3 X Time (years)	0.93	(0.88, 0.98)	0.010*	0.93	(0.88, 0.98)	0.010*
Exhaustion (Maastricht)						
Baseline Differences (ref: Class 1)						
Class 2	1.28	(0.95, 1.72)	0.102	1.17	(0.87, 1.56)	0.300
Class 3	1.99	(1.49, 2.67)	<.001***	1.65	(1.24, 2.20)	0.001**
Time (years)	1.20	(1.14, 1.25)	<.001***	1.13	(1.05, 1.21)	0.001**
Longitudinal Differences						
Class 2 X Time (years)	0.98	(0.92, 1.03)	0.391	0.96	(0.91, 1.02)	0.222
Class 3 X Time (years)	0.99	(0.93, 1.05)	0.747	0.98	(0.93, 1.04)	0.519
Grip Weakness						
Baseline Differences (ref: Class 1)						
Class 2	0.86	(0.62, 1.20)	0.387	0.86	(0.62, 1.20)	0.365
Class 3	0.96	(0.69, 1.34)	0.804	0.97	(0.69, 1.36)	0.864
Time (years)	0.96	(0.88, 1.05)	0.398	0.88	(0.77, 1.01)	0.076
Longitudinal Differences						
Class 2 X Time (years)	1.13	(1.01, 1.25)	0.026*	1.13	(1.02, 1.26)	0.023*
Class 3 X Time (years)	1.06	(0.95, 1.18)	0.291	1.05	(0.94, 1.17)	0.370

Note: n=3,068; p<.05*, p<.01**, p<.001***

Class 1 = High Intellectual/Social activity, Class 2 = High Social/Less Intellectual activity, Class 3 = Less Intellectual/Social activity, OR = odds ratio, CI = confidence interval, CES-D = Center for Epidemiologic Studies Depression Scale

Odds ratios for class indicators (e.g., "Class 2") represent difference in odds of the frailty symptom between that class and Class 1 at baseline for an "average" participant (random intercept is 0).

Odds ratios for class by time indicators (e.g., "Class 2 X Time (years)") represent change in odds ratios of the frailty symptom between that class and Class 1 per year in study for an "average" participant (random intercept and slope is 0).

Model 1 is unadjusted for covariates. Model 2 is adjusted for age, age by time interaction, sex, sex by time interaction, study site, study site by time interaction, race, education, treatment group, significant depressive symptoms (CES-D≥10), and number of medical comorbidities.

Supplemental Table 6.2: Baseline and longitudinal differences in physical frailty criteria by activity class, adjusted for prevalent Mild Cognitive Impairment

	Model 1 (Baseline MCI)			Model 2 (Baseline MCI & MCI by Time)		
Physical Frailty Criteria	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Slow Gait (>=7 sec)						
Baseline Differences						
(ref: Class 1)						
Class 2	2.90	(1.46, 5.75)	0.002**	2.90	(1.46, 5.76)	0.002**
Class 3	1.93	(1.05, 3.53)	0.034*	1.92	(1.05, 3.52)	0.034*
Class 4	3.78	(2.05, 6.95)	<.001***	3.75	(2.03, 6.90)	<.001***
Time (years)	1.35	(1.13, 1.60)	0.001**	1.36	(1.14, 1.62)	0.001**
Longitudinal Differences						
Class 2 X Time (years)	0.85	(0.73, 1.00)	0.049*	0.85	(0.73, 1.00)	0.048*
Class 3 X Time (years)	0.92	(0.81, 1.06)	0.257	0.92	(0.81, 1.06)	0.262
Class 4 X Time (years)	0.93	(0.81, 1.07)	0.331	0.94	(0.81, 1.08)	0.352
Prevalent MCI	2.84	(1.93, 4.18)	<.001***	3.07	(1.87, 5.05)	<.001***
Prev. MCI X Time (years)				0.97	(0.85, 1.10)	0.611
Exhaustion (Fried et al., 2001)						
Baseline Differences						
(ref: Class 1)						
Class 2	1.11	(0.79, 1.55)	0.542	1.11	(0.80, 1.56)	0.527
Class 3	1.12	(0.85, 1.49)	0.421	1.12	(0.84, 1.49)	0.436
Class 4	1.74	(1.30, 2.33)	<.001***	1.72	(1.28, 2.31)	<.001***
Time (years)	1.12	(1.04, 1.21)	0.002**	1.14	(1.06, 1.23)	0.001**
Longitudinal Differences						
Class 2 X Time (years)	0.96	(0.89, 1.04)	0.331	0.96	(0.89, 1.04)	0.305
Class 3 X Time (years)	0.98	(0.92, 1.05)	0.613	0.98	(0.92, 1.05)	0.631
Class 4 X Time (years)	0.93	(0.87, 1.00)	0.042*	0.94	(0.88, 1.00)	0.058
Prevalent MCI	1.74	(1.38, 2.18)	<.001***	2.00	(1.53, 2.61)	<.001***
Prev. MCI X Time (years)				0.93	(0.87, 1.00)	0.041*
Exhaustion (Maastricht)						
Baseline Differences						
(ref: Class 1)						
Class 2	1.21	(0.83, 1.76)	0.329	1.21	(0.83, 1.76)	0.325
Class 3	1.21	(0.88, 1.67)	0.249	1.21	(0.87, 1.67)	0.253
Class 4	1.61	(1.15, 2.27)	0.006**	1.60	(1.14, 2.25)	0.006**
Time (years)	1.14	(1.06, 1.23)	<.001***	1.15	(1.07, 1.24)	<.001***
Longitudinal Differences						
Class 2 X Time (years)	0.94	(0.88, 1.01)	0.078	0.99	(0.92, 1.07)	0.776
Class 3 X Time (years)	0.95	(0.89, 1.02)	0.140	0.94	(0.89, 1.01)	0.086
Class 4 X Time (years)	0.99	(0.92, 1.07)	0.789	0.95	(0.89, 1.02)	0.168
Prevalent MCI	1.62	(1.24, 2.12)	<.001***	1.75	(1.28, 2.40)	<.001***
Prev. MCI X Time (years)				0.97	(0.90, 1.04)	0.347
Weakness						
Baseline Differences						
(ref: Class 1)						
Class 2	1.08	(0.70, 1.66)	0.718	1.08	(0.70, 1.66)	0.720

Class 3	0.90	(0.62, 1.30)	0.580	0.90	(0.63, 1.31)	0.592
Class 4	0.86	(0.58, 1.27)	0.442	0.86	(0.58, 1.28)	0.457
Time (years)	0.92	(0.80, 1.05)	0.215	0.91	(0.80, 1.05)	0.189
Longitudinal Differences						
Class 2 X Time (years)	0.94	(0.82, 1.08)	0.360	0.94	(0.82, 1.08)	0.364
Class 3 X Time (years)	1.07	(0.96, 1.21)	0.225	1.07	(0.96, 1.20)	0.236
Class 4 X Time (years)	1.07	(0.94, 1.21)	0.305	1.06	(0.94, 1.20)	0.322
Prevalent MCI	1.05	(0.77, 1.43)	0.755	0.98	(0.67, 1.43)	0.911
Prev. MCI X Time (years)				1.04	(0.92, 1.19)	0.521

Note: n=3,068; $p<.05$*, $p<.01$**, $p<.001$***

Class 1 = High Intellectual/Social activity, Class 2 = High Social/Less Intellectual activity, Class 3 = Less Intellectual/Social activity, OR = odds ratio, CI = confidence interval, CES-D = Center for Epidemiologic Studies Depression Scale

Odds ratios for class indicators (e.g., "Class 2") represent difference in odds of the frailty symptom between that class and Class 1 at baseline for an "average" participant (random intercept is 0).

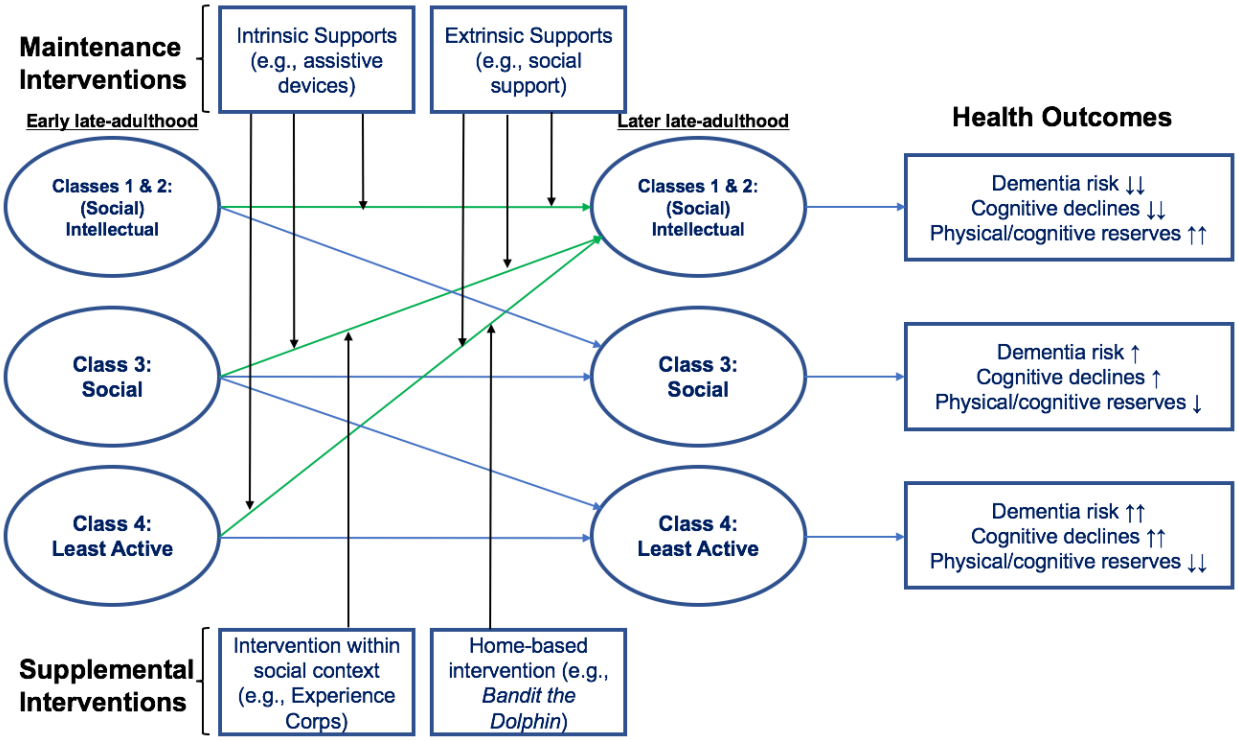
Odds ratios for class by time indicators (e.g., "Class 2 X Time (years)") represent change in odds ratios of the frailty symptom between that class and Class 1 per year in study for an "average" participant (random intercept and slope is 0).

Model 1 is adjusted for age, age by time interaction, sex, sex by time interaction, study site, study site by time interaction, race, education, treatment group, significant depressive symptoms (CES-D≥10), number of medical comorbidities, and prevalent Mild Cognitive Impairment at baseline. Model 2 is further adjusted for the interaction between prevalent MCI at baseline and time.

Table 7.1: Summary of activity characteristics, health outcomes, and relevant interventions for lifestyle engagement groups

Lifestyle Engagement Group	Activity Characteristics	Health Outcomes	Relevant Interventions
Class 1: Social Intellectual	High engagement broadly in intellectual and social activities	(Reference)	Intrinsic/extrinsic supports to maintain activity (relevant for each class)
Class 2: Intellectual	High engagement in select intellectual activities (e.g., viewing art, computer) Low engagement in social institutional activities (e.g., church)	1. No difference in risk for dementia 2. No difference in baseline cognitive functioning 3. Higher annual declines in visuospatial construction 4. Higher risk of baseline slow gait 5. Risk trajectory for slow gait converged over time	Socially-demanding intervention nested within an intellectual context Example: Senior Odyssey (Stine-Morrow et al., 2007)
Class 3: Social	High engagement in social institutional activities (e.g., church, volunteering) Low engagement in intellectual activities	1. Higher risk for dementia 2. Lower baseline cognitive performance in every domain 3. No difference in annual declines in cognition 4. Higher risk of baseline slow gait 5. No differences in risk trajectories for physical frailty criteria	Cognitively-demanding intervention nested within a community context Example: Experience Corps (Fried et al., 2004)
Class 4: Least Active	Low engagement broadly in intellectual and social activities Like other classes, high engagement in certain home-based activities (e.g., reading)	1. Highest risk for dementia 2. Lowest baseline cognitive performance in every domain 3. Higher annual declines in memory, attention, and visuospatial construction 4. Highest risk of baseline slow gait and exhaustion 5. Risk trajectory for exhaustion converged over time	Cognitively-demanding intervention nested within a home environment Example: *Bandit the Dolphin* (Carlson et al., in preparation)

Figure 7.1: Framework for encouraging later-life activity through maintenance and supplemental interventions



Note. Figure above illustrates possible changes in activity from early to later late-adulthood, where individuals can transition into more or less active groups over time (Classes 1 and 2 combined for simplicity). Maintenance interventions can be used to sustain current activity engagement by supporting life-space mobility. Supplemental interventions can be used to provide additional engagement that can provide a more cognitively- or socially-enriched lifestyle. Membership in lifestyle groups in later life is associated with risk of cognitive and physical health outcomes.

Appendices

Appendix 1: Lifestyle Activity Questionnaire

In the past year, have you spent your time (5=Everyday 4=A few times a week 3=Once a week 2=2 to 3 times a mo. 1=Once a month 0=< 1/mo. or never):

	Item	Abbreviation	Parisi et al. (2014) Domain Category
1	Doing things like sewing, mending, decorating, fixing things, or building?	Sewing	Creative
2	Cooking, baking or barbecuing?	Cooking	Creative
3	Singing or playing a musical instrument?	Sing/Instrument	Creative
4	Drawing or painting?	Drawing	Creative
5	Looking at paintings or other art?	View Art	Creative
6	Reading a newspaper?	Newspaper	Intellectual
7	Reading a book?	Books	Intellectual
8	Talking about local or national problems or issues?	Issues	Intellectual
9	Doing crossword puzzles?	CW Puzzles	Intellectual
10	Balancing your checkbook?	Checkbook	Intellectual
11	Taking courses or classes (credit or non-credit)?	Courses	Intellectual
12	Using a computer for word processing or for email/internet access?	Computer	Intellectual
13	Listening to music?	Radio (Music)	Passive
14	Listening to the radio (other than to music)?	Radio (not music)	Passive
15	Watching TV?	TV	Passive
16	Working in your garden, as permitted by the weather?	Gardening	Physical
17	Hunting, Fishing, Camping	Hunt/Camp	Physical
18	Shopping (grocery store, hardware store, mall outlets)?	Shopping	Physical
19	Going to the movies?	Movies	Social
20	Going to plays or concerts?	Concerts	Social
21	Attending church or other religious services?	Church	Social
22	Participating in a church, social or civic club or organization?	Social club	Social
23	Having people visit at your home, or visiting at someone else's home?	Visiting	Social
24	Assisting family members or family on regular basis? (ex. caring for them or doing errands)	Assist family	Social
25	Playing cards or games with others?	Playing cards	Social
26	Doing volunteer work?	Volunteering	Social

Appendix 2: Modified Center for Epidemiologic Studies Depression Scale (CES-D)

How often have you felt the following during the <u>past week</u>?
(0 = rarely/none of the time (less than 1 day), 1 = some or a little of the time (1 to 2 days), 2 = a moderate amount of time (2 to 4 days), 3 = most of the time, 9 = refused/don't know)

1. I was bothered by things that usually don't bother me.
2. I had trouble keeping my mind on what I was doing.
3. I felt everything I did was an effort.
4. I felt depressed.
5. I felt hopeful about the future.
6. I felt fearful.
7. My sleep was restless.
8. I was happy.
9. I felt lonely.
10. I could not get going.

Appendix 3: Ten semi-random samples for repeated latent class analyses.

	Semi-random Sample				
Type	One	Two	Three	Four	Five
Intellectual (4)	Drawing	CW Puzzles	View Art	Drawing	Sing/Paint
	Sing/Paint	View Art	Computer	Courses	CW Puzzles
	Sewing	Computer	Sewing	View Art	View Art
	Books	Sewing	Books	Sewing	Computer
Physical (1)	Gardening	Gardening	Walking	Gardening	Walking
Social (4)	Movies	Movies	Babysitting	Movies	Babysitting
	Babysitting	Babysitting	Social clubs	Playing Cards	Concerts
	Playing Cards	Concerts	Attend church	Social clubs	Playing Cards
	Volunteering	Assist family	Assist family	Attend church	Attend church
Type	Six	Seven	Eight	Nine	Ten
Intellectual (4)	Sing/Paint	Courses	Drawing	Courses	Sing/Paint
	CW Puzzles	View Art	Courses	CW Puzzles	View Art
	View Art	Sewing	CW Puzzles	Computer	Sewing
	Computer	Books	Books	Books	Books
Physical (1)	Walking	Walking	Gardening	Walking	Gardening
Social (4)	Volunteering	Movies	Movies	Concerts	Babysitting
	Social clubs	Babysitting	Babysitting	Playing Cards	Concerts
	Attend church	Social clubs	Concerts	Volunteering	Playing Cards
	Assist family	Assist family	Attend church	Social clubs	Volunteering

Note. Four intellectual, one physical, and four social activities chosen at random for each set.
CW = crossword

References

Aartsen, M. J., Smits, C. H. M., van Tilburg, T., Knipscheer, K. C. P. M., & Deeg, D. J. H. (2002). Activity in Older AdultsCause or Consequence of Cognitive Functioning? A Longitudinal Study on Everyday Activities and Cognitive Performance in Older Adults. *The Journals of Gerontology: Series B*, *57*(2), P153–P162. https://doi.org/10.1093/geronb/57.2.P153

Albert, M., Moss, M. B., Blacker, D., Tanzi, R., & McArdle, J. J. (2007). Longitudinal change in cognitive performance among individuals with mild cognitive impairment. *Neuropsychology*, *21*(2), 158–169. https://doi.org/10.1037/0894-4105.21.2.158

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. https://doi.org/10.1016/j.jalz.2011.03.008

Allman, R. M., Sawyer, P., & Roseman, J. M. (2006). The UAB Study of Aging: Background and insights into life-space mobility among older Americans in rural and urban settings. *Aging Health*, *2*(3), 417–429. https://doi.org/10.2217/1745509X.2.3.417

Alzheimer's Association. (2019). Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, *15*(3), 321–387.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR* (4th ed.). American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition). American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Appels, A., Höppener, P., & Mulder, P. (1987). A questionnaire to assess premonitory symptoms of myocardial infarction. *International Journal of Cardiology*, *17*(1), 15–24. https://doi.org/10.1016/0167-5273(87)90029-5

Appels, A., & Mulder, P. (1988). Excess fatigue as a precursor of myocardial infarction. *European Heart Journal*, *9*(7), 758–764. https://doi.org/10.1093/eurheartj/9.7.758

Army International Test Battery. (1944). *Manual of directions and scoring.* War Department, Adjutant General's Office.

Avlund, K., Lund, R., Holstein, B. E., & Due, P. (2004). Social relations as determinant of onset of disability in aging. *Archives of Gerontology and Geriatrics*, *38*(1), 85–99. https://doi.org/10.1016/j.archger.2003.08.003

Azevedo, M. R., Araújo, C. L. P., Reichert, F. F., Siqueira, F. V., da Silva, M. C., & Hallal, P. C. (2007). Gender differences in leisure-time physical activity. *International Journal of Public Health*, *52*(1), 8. https://doi.org/10.1007/s00038-006-5062-1

Baker, P. S., Bodner, E. V., & Allman, R. M. (2003). Measuring Life-Space Mobility in Community-Dwelling Older Adults. *Journal of the American Geriatrics Society*, *51*(11), 1610–1614. https://doi.org/10.1046/j.1532-5415.2003.51512.x

Baltes, P. B. (1987). Theoretical propositions of life-span developmental psychology: On the dynamics between growth and decline. *Developmental Psychology*, *23*(5), 611–626. https://doi.org/10.1037/0012-1649.23.5.611

Bandeen-Roche, K., Gross, A. L., Varadhan, R., Buta, B., Carlson, M. C., Huisingh-Scheetz, M., McAdams-DeMarco, M., Piggott, D. A., Brown, T. T., Hasan, R. K., Kalyani, R. R., Seplaki, C. L., Walston, J. D., & Xue, Q.-L. (2019). Principles and Issues for Physical Frailty Measurement and its Clinical Application. *The Journals of Gerontology: Series A*, glz158. https://doi.org/10.1093/gerona/glz158

Bandeen-Roche, K., Seplaki, C. L., Huang, J., Buta, B., Kalyani, R. R., Varadhan, R., Xue, Q.-L., Walston, J. D., & Kasper, J. D. (2015). Frailty in Older Adults: A Nationally Representative Profile in the United States. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *70*(11), 1427–1434. https://doi.org/10.1093/gerona/glv133

Bandeen-Roche, K., Xue, Q.-L., Ferrucci, L., Walston, J., Guralnik, J. M., Chaves, P., Zeger, S. L., & Fried, L. P. (2006). Phenotype of Frailty: Characterization in the Women's Health and Aging Studies. *The Journals of Gerontology: Series A*, *61*(3), 262–266. https://doi.org/10.1093/gerona/61.3.262

Barnes, J., Bartlett, J. W., van de Pol, L. A., Loy, C. T., Scahill, R. I., Frost, C., Thompson, P., & Fox, N. C. (2009). A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. *Neurobiology of Aging*, *30*(11), 1711–1723. https://doi.org/10.1016/j.neurobiolaging.2008.01.010

Barnes, L. L., Mendes de Leon, C. F., Bienias, J. L., & Evans, D. A. (2004). A longitudinal study of black–white differences in social resources. *The Journals of Gerontology: Series B*, *59*(3), S146–S153. https://doi.org/10.1093/geronb/59.3.S146

Bartels, S. J., & Naslund, J. A. (2013). The underside of the Silver Tsunami—Older adults and mental health care. *New England Journal of Medicine*, *368*(6), 493–496. https://doi.org/10.1056/NEJMp1211456

Becker, J. T., Boller, F., Saxton, J., & McGonigle-Gibson, K. L. (1987). Normal rates of forgetting of verbal and non-verbal material in Alzheimer's Disease. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior*, *23*(1), 59–72. https://doi.org/10.1016/S0010-9452(87)80019-9

Bennett, D. A., Arnold, S. E., Valenzuela, M. J., Brayne, C., & Schneider, J. A. (2014). Cognitive and social lifestyle: Links with neuropathology and cognition in late life. *Acta Neuropathologica*, *127*(1), 137–150. https://doi.org/10.1007/s00401-013-1226-2

Bennett, D. A., Schneider, J. A., Tang, Y., Arnold, S. E., & Wilson, R. S. (2006). The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: A longitudinal cohort study. *The Lancet Neurology*, *5*(5), 406–412. https://doi.org/10.1016/S1474-4422(06)70417-3

Berkman, L. F., Glass, T., Brissette, I., & Seeman, T. E. (2000). From social integration to health: Durkheim in the new millennium. *Social Science & Medicine*, *51*(6), 843–857. https://doi.org/10.1016/S0277-9536(00)00065-4

Berkman, L. F., Seeman, T. E., Albert, M., Blazer, D., Kahn, R., Mohs, R., Finch, C., Schneider, E., Cotman, C., McClearn, G., Nesselroade, J., Featherman, D., Garmezy, N., McKhann, G., Brim, G., Prager, D., & Rowe, J. (1993). High, usual and impaired functioning in community-dwelling older men and women: Findings from the MacArthur Foundation Research Network on successful aging. *Journal of Clinical Epidemiology*, *46*(10), 1129–1140. https://doi.org/10.1016/0895-4356(93)90112-E

Berney, L. R., & Blane, D. B. (1997). Collecting retrospective data: Accuracy of recall after 50 years judged against historical records. *Social Science & Medicine (1982)*, *45*(10), 1519–1525.

Bielak, A. A. M. (2010). How can we not 'lose it' if we still don't understand how to 'use it'? Unanswered questions about the influence of activity participation on cognitive performance in older age – a mini-review. *Gerontology*, *56*(5), 507–519. https://doi.org/10.1159/000264918

Bielak, A. A. M. (2017). Different perspectives on measuring lifestyle engagement: A comparison of activity measures and their relation with cognitive performance in older adults. *Aging, Neuropsychology, and Cognition*, *24*(4), 435–452. https://doi.org/10.1080/13825585.2016.1221378

Bielak, A. A. M., Anstey, K. J., Christensen, H., & Windsor, T. D. (2012). Activity engagement is related to level, but not change in cognitive ability across adulthood. *Psychology and Aging*, *27*(1), 219–228. https://doi.org/10.1037/a0024667

Bielak, A. A. M., Gerstorf, D., Anstey, K. J., & Luszcz, M. A. (2014). Longitudinal associations between activity and cognition vary by age, activity type, and cognitive domain. *Psychology and Aging*, *29*(4), 863–872. https://doi.org/10.1037/a0036960

Bielak, A. A. M., Hughes, T. F., Small, B. J., & Dixon, R. A. (2007). It's Never Too Late to Engage in Lifestyle Activities: Significant Concurrent but not Change Relationships Between Lifestyle Activities and Cognitive Speed. *The Journals of Gerontology: Series B*, *62*(6), P331–P339. https://doi.org/10.1093/geronb/62.6.P331

Bielak, A. A. M., Mogle, J., & Sliwinski, M. J. (2017). What did you do today? Variability in daily activities is related to variability in daily cognitive performance. *The Journals of Gerontology: Series B*. https://doi.org/10.1093/geronb/gbx145

Björgvinsson, T., Kertz, S. J., Bigda-Peyton, J. S., McCoy, K. L., & Aderka, I. M. (2013). Psychometric properties of the CES-D-10 in a psychiatric sample. *Assessment*, *20*(4), 429–436. https://doi.org/10.1177/1073191113481998

Bolck, A., Croon, M., & Hagenaars, J. (2004). Estimating Latent Structure Models with Categorical Variables: One-Step Versus Three-Step Estimators. *Political Analysis*, *12*(01), 3–27. https://doi.org/10.1093/pan/mph001

Booth, M. L., Owen, N., Bauman, A., Clavisi, O., & Leslie, E. (2000). Social–Cognitive and Perceived Environment Influences Associated with Physical Activity in Older Australians. *Preventive Medicine*, *31*(1), 15–22. https://doi.org/10.1006/pmed.2000.0661

Bowie, J., Juon, H. S., Taggart, T., Thorpe, R. J., & Ensminger, M. (2017). Predictors of religiosity in a cohort of African Americans. *Race and Social Problems*, *9*(1), 29–41. https://doi.org/10.1007/s12552-016-9189-2

Boyle, P. A., Buchman, A. S., Barnes, L. L., & Bennett, D. A. (2010). Effect of a purpose in life on risk of incident Alzheimer disease and Mild Cognitive Impairment in community-dwelling older persons. *Archives of General Psychiatry*, *67*(3), 304. https://doi.org/10.1001/archgenpsychiatry.2009.208

Branch, L. G., Katz, S., Kniepmann, K., & Papsidero, J. A. (1984). A prospective study of functional status among community elders. *American Journal of Public Health*, *74*(3), 266–268. https://doi.org/10.2105/AJPH.74.3.266

Breslow, N. E., & Clayton, D. G. (1993). Approximate Inference in Generalized Linear Mixed Models. *Journal of the American Statistical Association*, *88*(421), 9–25. JSTOR. https://doi.org/10.2307/2290687

Brookmeyer, R., Abdalla, N., Kawas, C. H., & Corrada, M. M. (2018). Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. *Alzheimer's & Dementia*, *14*(2), 121–129. https://doi.org/10.1016/j.jalz.2017.10.009

Buchman, A. S., Boyle, P. A., Wilson, R. S., Fleischman, D. A., Leurgans, S., & Bennett, D. A. (2009). Association between late-life social activity and motor decline in older adults. *Archives of Internal Medicine*, *169*(12), 1139. https://doi.org/10.1001/archinternmed.2009.135

Buchman, A. S., Wilson, R. S., Yu, L., James, B. D., Boyle, P. A., & Bennett, D. A. (2014). Total daily activity declines more rapidly with increasing age in older adults. *Archives of Gerontology and Geriatrics*, *58*(1), 74–79. https://doi.org/10.1016/j.archger.2013.08.001

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. https://doi.org/10.1016/j.neuron.2004.09.006

Burnham, K. P., & Anderson, D. R. (2004). Multimodel Inference: Understanding AIC and BIC in Model Selection. *Sociological Methods & Research*, *33*(2), 261–304. https://doi.org/10.1177/0049124104268644

Carlson, M. C. (2011). Introduction: A life course perspective on activity and neurocognitive health. *Journal of the International Neuropsychological Society*, *17*(6), 970–974. https://doi.org/10.1017/S1355617711001366

Carlson, M. C., Erickson, K. I., Kramer, A. F., Voss, M. W., Bolea, N., Mielke, M., McGill, S., Rebok, G. W., Seeman, T., & Fried, L. P. (2009). Evidence for neurocognitive plasticity in at-risk older adults: The experience corps program. *The Journals of Gerontology: Series A*, *64A*(12), 1275–1282. https://doi.org/10.1093/gerona/glp117

Carlson, M. C., Kuo, J. H., Chuang, Y.-F., Varma, V., Harris, G., Albert, M., Erickson, K. I., Kramer, A. F., Parisi, J. M., Xue, Q.-L., Tan, E., Tanner, E. K., Gross, A., Seeman, T. E., Gruenewald, T., McGill, S., Rebok, G. W., & Fried, L. P. (2015). Impact of the Baltimore Experience Corps Trial

on cortical and hippocampal volumes. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *11*(11), 1340–1348. https://doi.org/10.1016/j.jalz.2014.12.005

Carlson, M. C., Parisi, J. M., Xia, J., Xue, Q.-L., Rebok, G. W., Bandeen-Roche, K., & Fried, L. P. (2012). Lifestyle activities and memory: Variety may be the spice of life. The Women's Health and Aging Study II. *Journal of the International Neuropsychological Society : JINS*, *18*(2), 286–294. https://doi.org/10.1017/S135561771100169X

Carlson, M. C., & Varma, V. R. (2015). Activity and Neurocognitive Health in Older Adults. In S. R. Waldstein & M. F. Elias (Eds.), *Neuropsychology of Cardiovascular Disease*. Psychology Press.

Carlson, M. C., Xue, Q.-L., Zhou, J., & Fried, L. P. (2009). Executive Decline and Dysfunction Precedes Declines in Memory: The Women's Health and Aging Study II. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *64A*(1), 110–117. https://doi.org/10.1093/gerona/gln008

Chan, T., Parisi, J. M., Moored, K. D., & Carlson, M. C. (2018). Variety of enriching early-life activities linked to late-life cognitive functioning in urban community-dwelling African Americans. *The Journals of Gerontology: Series B*. https://doi.org/10.1093/geronb/gby056

Chui, H. C., Mack, W., Jackson, J. E., Mungas, D., Reed, B. R., Tinklenberg, J., Chang, F.-L., Skinner, K., Tasaki, C., & Jagust, W. J. (2000). Clinical Criteria for the Diagnosis of Vascular Dementia: A Multicenter Study of Comparability and Interrater Reliability. *Archives of Neurology*, *57*(2), 191–196. https://doi.org/10.1001/archneur.57.2.191

Clark, L. R., Schiehser, D. M., Weissberger, G. H., Salmon, D. P., Delis, D. C., & Bondi, M. W. (2012). Specific Measures of Executive Function Predict Cognitive Decline in Older Adults. *Journal of the International Neuropsychological Society*, *18*(1), 118–127. https://doi.org/10.1017/S1355617711001524

Collins, L. M., & Lanza, S. T. (2010). *Latent Class and Latent Transition Analysis: With Applications in the Social, Behavioral, and Health Sciences*. John Wiley & Sons.

Crimmins, E. M., Zhang, Y., & Saito, Y. (2016). Trends Over 4 Decades in Disability-Free Life Expectancy in the United States. *American Journal of Public Health*, *106*(7), 1287–1293. https://doi.org/10.2105/AJPH.2016.303120

DeKosky, S. T. (2008). Ginkgo biloba for Prevention of Dementia: A Randomized Controlled Trial. *JAMA*, *300*(19), 2253. https://doi.org/10.1001/jama.2008.683

DeKosky, S. T., Fitzpatrick, A., Ives, D. G., Saxton, J., Williamson, J., Lopez, O. L., Burke, G., Fried, L., Kuller, L. H., Robbins, J., Tracy, R., Woolard, N., Dunn, L., Kronmal, R., Nahin, R., & Furberg, C. (2006). The Ginkgo Evaluation of Memory (GEM) study: Design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. *Contemporary Clinical Trials*, *27*(3), 238–253. https://doi.org/10.1016/j.cct.2006.02.007

DeKosky, S. T., Williamson, J. D., Fitzpatrick, A. L., Kronmal, R. A., Ives, D. G., Saxton, J. A., Lopez, O. L., Burke, G., Carlson, M. C., Fried, L. P., Kuller, L. H., Robbins, J. A., Tracy, R. P., Woolard, N. F., Dunn, L., Snitz, B. E., Nahin, R. L., & Furberg, C. D. (2008). Ginkgo biloba for Prevention of Dementia: A Randomized Controlled Trial. *JAMA*, *300*(19), 2253–2262. https://doi.org/10.1001/jama.2008.683

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *The California Verbal Learning Test*. Psychological Corporation.

Dixon, R. A., & Bäckman, L. (1995). Concepts of compensation: Integrated, differentiated, and Janus-faced. In *Compensating for psychological deficits and declines: Managing losses and promoting gains* (pp. 3–19). Lawrence Erlbaum Associates, Inc.

Downey, R. G., & King, C. V. (1998). Missing Data in Likert Ratings: A Comparison of Replacement Methods. *The Journal of General Psychology*, *125*(2), 175–191. https://doi.org/10.1080/00221309809595542

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., & May, A. (2004). Neuroplasticity: Changes in grey matter induced by training. *Nature*, *427*(6972), 311–312. https://doi.org/10.1038/427311a

Dziak, J. J., Lanza, S. T., & Tan, X. (2014). Effect Size, Statistical Power, and Sample Size Requirements for the Bootstrap Likelihood Ratio Test in Latent Class Analysis. *Structural Equation Modeling: A Multidisciplinary Journal*, *21*(4), 534–552. https://doi.org/10.1080/10705511.2014.919819

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J., Martin, S. A., Pence, B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences*, *108*(7), 3017–3022. https://doi.org/10.1073/pnas.1015950108

Ericsson, K. A., & Chamess, N. (1994). Expert performance: Its structure and acquisition. *American Psychologist*, *49*(8), 725–747.

Erkinjuntti, T. (1994). Clinical Criteria for Vascular Dementia: The NINDS-AIREN Criteria. *Dementia and Geriatric Cognitive Disorders*, *5*(3–4), 189–192. https://doi.org/10.1159/000106721

Everard, K. M., Lach, H. W., Fisher, E. B., & Baum, M. C. (2000). Relationship of activity and social support to the functional health of older adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *55*(4), S208–S212. https://doi.org/10.1093/geronb/55.4.S208

Farias, S. T., Cahn-Weiner, D. A., Harvey, D. J., Reed, B. R., Mungas, D., Kramer, J. H., & Chui, H. (2009). Longitudinal Changes in Memory and Executive Functioning are Associated with longitudinal change in instrumental activities of daily living in older Adults. *The Clinical Neuropsychologist*, *23*(3), 446–461. https://doi.org/10.1080/13854040802360558

Ferrucci, L., & Fabbri, E. (2018). Inflammageing: Chronic inflammation in ageing, cardiovascular disease, and frailty. *Nature Reviews Cardiology*, *15*(9), 505–522. https://doi.org/10.1038/s41569-018-0064-2

Fitzpatrick, A. L., Fried, L. P., Williamson, J., Crowley, P., Posey, D., Kwong, L., Bonk, J., Moyer, R., Chabot, J., Kidoguchi, L., Furberg, C. D., & DeKosky, S. T. (2006). Recruitment of the elderly

into a pharmacologic prevention trial: The Ginkgo Evaluation of Memory Study experience. *Contemporary Clinical Trials*, *27*(6), 541–553. https://doi.org/10.1016/j.cct.2006.06.007

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., & De Benedictis, G. (2006). Inflamm-aging: An Evolutionary Perspective on Immunosenescence. *Annals of the New York Academy of Sciences*, *908*(1), 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x

Fratiglioni, L., Paillard-Borg, S., & Winblad, B. (2004). An active and socially integrated lifestyle in late life might protect against dementia. *The Lancet Neurology*, *3*(6), 343–353. https://doi.org/10.1016/S1474-4422(04)00767-7

Fried, L. P., Bandeen-Roche, K., Chaves, P. H. M., & Johnson, B. A. (2000). Preclinical mobility disability predicts incident mobility disabilityin older women. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *55*(1), M43–M52. https://doi.org/10.1093/gerona/55.1.M43

Fried, L. P., Borhani, N. O., Enright, P., Furberg, C. D., Gardin, J. M., Kronmal, R. A., Kuller, L. H., Manolio, T. A., Mittelmark, M. B., Newman, A., O'Leary, D. H., Psaty, B., Rautaharju, P., Tracy, R. P., & Weiler, P. G. (1991). The cardiovascular health study: Design and rationale. *Annals of Epidemiology*, *1*(3), 263–276. https://doi.org/10.1016/1047-2797(91)90005-W

Fried, L. P., Carlson, M. C., Freedman, M., Frick, K. D., Glass, T. A., Hill, J., McGill, S., Rebok, G. W., Seeman, T., Tielsch, J., Wasik, B. A., & Zeger, S. (2004). A social model for health promotion for an aging population: Initial evidence on the experience corps model. *Journal of Urban Health*, *81*(1), 64–78. https://doi.org/10.1093/jurban/jth094

Fried, L. P., Carlson, M. C., McGill, S., Seeman, T., Xue, Q.-L., Frick, K., Tan, E., Tanner, E. K., Barron, J., Frangakis, C., Piferi, R., Martinez, I., Gruenewald, T., Martin, B. K., Berry-Vaughn, L., Stewart, J., Dickersin, K., Willging, P. R., & Rebok, G. W. (2013). Experience Corps: A dual trial to promote the health of older adults and children's academic success. *Contemporary Clinical Trials*, *36*(1), 1–13. https://doi.org/10.1016/j.cct.2013.05.003

Fried, L. P., Ettinger, W. H., Lind, B., Newman, A. B., & Gardin, J. (1994). Physical disability in older adults: A physiological approach. *Journal of Clinical Epidemiology*, *47*(7), 747–760. https://doi.org/10.1016/0895-4356(94)90172-4

Fried, L. P., Kasper, J. D., Guralnik, J. M., & Simonsick, E. M. (1995). The women's health and aging study: An introduction. In *The Women's Health and Aging Study: Health and social characteristics of older women with disability.* (pp. 1–8). National Institute on Aging.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W. J., Burke, G., & McBurnie, M. A. (2001). Frailty in Older Adults: Evidence for a Phenotype. *The Journals of Gerontology: Series A*, *56*(3), M146–M157. https://doi.org/10.1093/gerona/56.3.M146

Fried, L. P., Young, Y., Rubin, G., & Bandeen-Roche, K. (2001). Self-reported preclinical disability identifies older women with early declines in performance and early disease. *Journal of Clinical Epidemiology*, *54*(9), 889–901. https://doi.org/10.1016/S0895-4356(01)00357-2

Gabriel, K. K. P., Morrow, J. R., & Woolsey, A.-L. T. (2012). Framework for Physical Activity as a Complex and Multidimensional Behavior. *Journal of Physical Activity and Health*, *9*(s1), S11–S18. https://doi.org/10.1123/jpah.9.s1.s11

Gagliardi, C., Spazzafumo, L., Marcellini, F., Mollenkopf, H., Ruoppila, I., Tacken, M., & Szémann, Z. (2007). The outdoor mobility and leisure activities of older people in five European countries. *Ageing and Society*, *27*(05), 683–700. https://doi.org/10.1017/S0144686X07006198

Gallo, J. J., Rebok, G. W., Tennsted, S., Wadley, V. G., Horgas, A., Independent, T. A. C. T. for, & Investigators, V. E. (Active) S. (2003). Linking depressive symptoms and functional disability in late life. *Aging & Mental Health*, *7*(6), 469–480. https://doi.org/10.1080/13607860310001594736

Ghisletta, P., Bickel, J.-F., & Lövdén, M. (2006). Does Activity Engagement Protect Against Cognitive Decline in Old Age? Methodological and Analytical Considerations. *The Journals of Gerontology: Series B*, *61*(5), P253–P261. https://doi.org/10.1093/geronb/61.5.P253

Glass, T. A. (1998). Conjugating the "tenses" of function: Discordance among hypothetical, experimental, and enacted function in older adults. *The Gerontologist*, *38*(1), 101–112. https://doi.org/10.1093/geront/38.1.101

Glass, T. A., De Leon, C. F. M., Bassuk, S. S., & Berkman, L. F. (2006). Social engagement and depressive symptoms in late life: Longitudinal findings. *Journal of Aging and Health*, *18*(4), 604–628. https://doi.org/10.1177/0898264306291017

Glover, S., & Dixon, P. (2004). Likelihood ratios: A simple and flexible statistic for empirical psychologists. *Psychonomic Bulletin & Review*, *11*(5), 791–806. https://doi.org/10.3758/BF03196706

Glymour, M. M., Weuve, J., Berkman, L. F., Kawachi, I., & Robins, J. M. (2005). When Is Baseline Adjustment Useful in Analyses of Change? An Example with Education and Cognitive Change. *American Journal of Epidemiology*, *162*(3), 267–278. https://doi.org/10.1093/aje/kwi187

Gordon, R. S. (1983). An operational classification of disease prevention. *Public Health Reports*, *98*(2), 107–109.

Gow, A. J., Avlund, K., & Mortensen, E. L. (2014). Leisure activity associated with cognitive ability level, but not cognitive change. *Frontiers in Psychology*, *5*. https://doi.org/10.3389/fpsyg.2014.01176

Gow, A. J., Pattie, A., & Deary, I. J. (2017). Lifecourse activity participation from early, mid, and later adulthood as determinants of cognitive aging: The Lothian Birth Cohort 1921. *The Journals of Gerontology: Series B*, *72*(1), 25–37. https://doi.org/10.1093/geronb/gbw124

Griffiths, R. A., Good, W. R., Watson, N. P., O'Donnell, H. F., Fell, P. J., & Shakespeare, J. M. (1987). Depression, dementia and disability in the elderly. *The British Journal of Psychiatry*, *150*(4), 482–493. https://doi.org/10.1192/bjp.150.4.482

Gross, A. L., Parisi, J. M., Spira, A. P., Kueider, A. M., Ko, J. Y., Saczynski, J. S., Samus, Q. M., & Rebok, G. W. (2012). Memory training interventions for older adults: A meta-analysis. *Aging & Mental Health*, *16*(6), 722–734. https://doi.org/10.1080/13607863.2012.667783

Gross, A. L., & Rebok, G. W. (2011). Memory Training and Strategy Use in Older Adults: Results from the ACTIVE Study. *Psychology and Aging*, *26*(3), 503–517. https://doi.org/10.1037/a0022687

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. https://doi.org/10.1093/gerona/glw067

Guralnik, J. M., Ferrucci, L., Pieper, C. F., Leveille, S. G., Markides, K. S., Ostir, G. V., Studenski, S., Berkman, L. F., & 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: Biological Sciences and Medical Sciences*, *55*(4), M221–M231. https://doi.org/10.1093/gerona/55.4.M221

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., Scherr, P. A., & Wallace, R. B. (1994). A Short Physical Performance Battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. *Journal of Gerontology*, *49*(2), M85–M94. https://doi.org/10.1093/geronj/49.2.M85

Haggerty, R. J., & Mrazek, P. J. (1994). *Reducing Risks for Mental Disorders: Frontiers for Preventive Intervention Research*. National Academies Press.

Harris, T., Kovar, M. G., Suzman, R., Kleinman, J. C., & Feldman, J. J. (1989). Longitudinal study of physical ability in the oldest-old. *American Journal of Public Health*, *79*(6), 698–702. https://doi.org/10.2105/AJPH.79.6.698

Heesch, K. C., Hill, R. L., Aguilar-Farias, N., van Uffelen, J. G. Z., & Pavey, T. (2018). Validity of objective methods for measuring sedentary behaviour in older adults: A systematic review. *International Journal of Behavioral Nutrition and Physical Activity*, *15*(1), 119. https://doi.org/10.1186/s12966-018-0749-2

Hernán, M. A., Hernández-Díaz, S., & Robins, J. M. (2004). A Structural Approach to Selection Bias. *Epidemiology*, *15*(5), 615–625. JSTOR.

Hertzog, C., Kramer, A. F., Wilson, R. S., & Lindenberger, U. (2009). 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. https://doi.org/10.1111/j.1539-6053.2009.01034.x

Hill, C. V., Pérez-Stable, E. J., Anderson, N. A., & Bernard, M. A. (2015). The National Institute on Aging health disparities research framework. *Ethnicity & Disease*, *25*(3), 245. https://doi.org/10.18865/ed.25.3.245

Hill, R. D., Wahlin, Å., Winblad, B., & Bäckman, L. (1995). The role of demographic and life style variables in utilizing cognitive support for episodic remembering among very old adults. *The Journals of Gerontology: Series B*, *50B*(4), P219–P227. https://doi.org/10.1093/geronb/50B.4.P219

Hogan, J. W., Roy, J., & Korkontzelou, C. (2004). Handling drop-out in longitudinal studies. *Statistics in Medicine*, *23*(9), 1455–1497. https://doi.org/10.1002/sim.1728

Holtzer, R., Epstein, N., Mahoney, J. R., Izzetoglu, M., & Blumen, H. M. (2014). Neuroimaging of mobility in aging: A targeted review. *The Journals of Gerontology: Series A*, *69*(11), 1375–1388. https://doi.org/10.1093/gerona/glu052

Hultsch, D. F., Hammer, M., & Small, B. J. (1993). Age Differences in Cognitive Performance in Later Life: Relationships to Self-Reported Health and Activity Life Style. *Journal of Gerontology*, *48*(1), P1–P11. https://doi.org/10.1093/geronj/48.1.P1

Hultsch, D. F., Hertzog, C., Small, B. J., & Dixon, R. A. (1999a). Use it or lose it: Engaged lifestyle as a buffer of cognitive decline in aging? *Psychology and Aging*, *14*(2), 245–263.

Hultsch, D. F., Hertzog, C., Small, B. J., & Dixon, R. A. (1999b). Use it or lose it: Engaged lifestyle as a buffer of cognitive decline in aging? *Psychology and Aging*, *14*(2), 245–263. https://doi.org/10.1037/0882-7974.14.2.245

Jack, C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., Shaw, L. M., Vemuri, P., Wiste, H. J., Weigand, S. D., Lesnick, T. G., Pankratz, V. S., Donohue, M. C., &

Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *The Lancet Neurology*, *12*(2), 207–216. https://doi.org/10.1016/S1474-4422(12)70291-0

James, B. D., Boyle, P. A., Buchman, A. S., Barnes, L. L., & Bennett, D. A. (2011). Life Space and Risk of Alzheimer Disease, Mild Cognitive Impairment, and Cognitive Decline in Old Age. *The American Journal of Geriatric Psychiatry*, *19*(11), 961–969. https://doi.org/10.1097/JGP.0b013e318211c219

James, B. D., Boyle, P. A., Buchman, A. S., & Bennett, D. A. (2011). Relation of late-life social activity with incident disability among community-dwelling older adults. *The Journals of Gerontology: Series A*, *66A*(4), 467–473. https://doi.org/10.1093/gerona/glq231

Jiang, J., Sachdev, P., Lipnicki, D. M., Zhang, H., Liu, T., Zhu, W., Suo, C., Zhuang, L., Crawford, J., Reppermund, S., Trollor, J., Brodaty, H., & Wen, W. (2014). A longitudinal study of brain atrophy over two years in community-dwelling older individuals. *NeuroImage*, *86*, 203–211. https://doi.org/10.1016/j.neuroimage.2013.08.022

Jobe, J. B., Smith, D. M., Ball, K., Tennstedt, S. L., Marsiske, M., Willis, S. L., Rebok, G. W., Morris, J. N., Helmers, K. F., Leveck, M. D., & Kleinman, K. (2001). ACTIVE: A Cognitive Intervention Trial to Promote Independence in Older Adults. *Controlled Clinical Trials*, *22*(4), 453–479.

Karbach, J., & Verhaeghen, P. (2014). Making working memory work: A meta-analysis of executive-control and working memory training in older adults. *Psychological Science*, *25*(11), 2027–2037. https://doi.org/10.1177/0956797614548725

Kenward, M. G., & Roger, J. H. (1997). Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. *Biometrics*, *53*(3), 983. https://doi.org/10.2307/2533558

Kerr, J., Marshall, S. J., Patterson, R. E., Marinac, C. R., Natarajan, L., Rosenberg, D., Wasilenko, K., & Crist, K. (2013). Objectively Measured Physical Activity is Related to Cognitive Function in Older Adults. *Journal of the American Geriatrics Society*, *61*(11). https://doi.org/10.1111/jgs.12524

Kim, H. K., & McKenry, P. C. (1998). Social networks and support: A comparison of African Americans, Asian Americans, Caucasians, and Hispanics. *Journal of Comparative Family Studies*, *29*(2), 313–334. JSTOR.

Kincade, J. E., Rabiner, D. J., Bernard, S. L., Woomert, A., Konrad, T. R., Defriese, G. H., & Ory, M. G. (1996). Older adults as a community resource: Results from the National Survey of Self-Care and Aging. *The Gerontologist*, *36*(4), 474–482. https://doi.org/10.1093/geront/36.4.474

King, A. C., Castro, C., Wilcox, S., Eyler, A. A., Sallis, J. F., & Brownson, R. C. (2000). Personal and environmental factors associated with physical inactivity among different racial-ethnic groups of U.S. middle-aged and older-aged women. *Health Psychology*, *19*(4), 354–364.

Kliegl, R., Smith, J., & Baltes, P. B. (1989). Testing-the-limits and the study of adult age differences in cognitive plasticity of a mnemonic skill. *Developmental Psychology*, *25*(2), 247–256. https://doi.org/10.1037/0012-1649.25.2.247

Kop, W. J., Appels, A. P., Mendes de Leon, C. F., de Swart, H. B., & Bär, F. W. (1994). Vital exhaustion predicts new cardiac events after successful coronary angioplasty.: *Psychosomatic Medicine*, *56*(4), 281–287. https://doi.org/10.1097/00006842-199407000-00001

Kopp, M. S., Falger, P. R. J., Appels, A., & Szedmak, S. (1998). Depressive Symptomatology and Vital Exhaustion Are Differentially Related to Behavioral Risk Factors for Coronary Artery Disease. *Psychosomatic Medicine*, *60*(6), 752–758.

Kramer, A. F., & Colcombe, S. (2018). Fitness Effects on the Cognitive Function of Older Adults: A Meta-Analytic Study—Revisited. *Perspectives on Psychological Science*, *13*(2), 213–217. https://doi.org/10.1177/1745691617707316

Laird, N. M., & Ware, J. H. (1982). Random-effects models for longitudinal data. *Biometrics*, *38*(4), 963–974.

Lanza, S. T., Coffman, D. L., & Xu, S. (2013). Causal Inference in Latent Class Analysis. *Structural Equation Modeling : A Multidisciplinary Journal*, *20*(3), 361–383. https://doi.org/10.1080/10705511.2013.797816

Lanza, S. T., Tan, X., & Bray, B. C. (2013). Latent Class Analysis With Distal Outcomes: A Flexible Model-Based Approach. *Structural Equation Modeling: A Multidisciplinary Journal*, *20*(1), 1–26. https://doi.org/10.1080/10705511.2013.742377

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *The Gerontologist*, *9*(3), 179–186.

Lennartsson, C., & Silverstein, M. (2001). Does engagement with life enhance survival of elderly people in sweden? The role of social and leisure activities. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *56*(6), S335–S342. https://doi.org/10.1093/geronb/56.6.S335

Lopez, O. L., Kuller, L. H., Fitzpatrick, A., Ives, D., Becker, J. T., & Beauchamp, N. (2003). Evaluation of Dementia in the Cardiovascular Health Cognition Study. *Neuroepidemiology*, *22*(1), 1–12. https://doi.org/10.1159/000067110

Manalel, J. A., Morris, E., Ryan, L. H., & Smith, J. (2018). SOCIAL INTEGRATION THROUGH ACTIVITY ENGAGEMENT: LONG-TERM EFFECTS ON COGNITION. *Innovation in Aging*, *2*(Suppl 1), 431. https://doi.org/10.1093/geroni/igy023.1615

Mayeda, E. R., Glymour, M. M., Quesenberry, C. P., & Whitmer, R. A. (2016). Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimer's & Dementia*, *12*(3), 216–224. https://doi.org/10.1016/j.jalz.2015.12.007

McDonough, I. M., Haber, S., Bischof, G. N., & Park, D. C. (2015). The Synapse Project: Engagement in mentally challenging activities enhances neural efficiency. *Restorative Neurology and Neuroscience*, *33*(6), 865–882. https://doi.org/10.3233/RNN-150533

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), 939–939. https://doi.org/10.1212/WNL.34.7.939

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia 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), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

Mendes de Leon, C. F., Glass, T. A., & Berkman, L. F. (2003). Social engagement and disability in a community population of older adults: The New Haven EPESE. *American Journal of Epidemiology*, *157*(7), 633–642. https://doi.org/10.1093/aje/kwg028

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. https://doi.org/10.1186/1471-2318-2-1

Mitnitski, A. B., Mogilner, A. J., & Rockwood, K. (2001). *Accumulation of Deficits as a Proxy Measure of Aging* [Research Article]. TheScientificWorld; Hindawi. https://doi.org/10.1100/tsw.2001.58

Mohs, R. C. (1996). The Alzheimer's Disease Assessment Scale. *International Psychogeriatrics*, *8*(2), 195–203. https://doi.org/10.1017/S1041610296002578

Moored, K. D., Chan, T., Varma, V. R., Chuang, Y.-F., Parisi, J. M., & Carlson, M. C. (2018). Engagement in enriching early-life activities is associated with larger hippocampal and amygdala volumes in community-dwelling older adults. *The Journals of Gerontology: Series B*. https://doi.org/10.1093/geronb/gby150

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology*, *43*(11), 2412–2414. https://doi.org/10.1212/WNL.43.11.2412-a

Najar, J., Östling, S., Gudmundsson, P., Sundh, V., Johansson, L., Kern, S., Guo, X., Hällström, T., & Skoog, I. (2019). Cognitive and physical activity and dementia: A 44-year longitudinal population study of women. *Neurology*, 10.1212/WNL.0000000000007021. https://doi.org/10.1212/WNL.0000000000007021

National Academies of Sciences, Engineering, and Medicine. (2017). *Preventing Cognitive Decline and Dementia: A Way Forward*. National Academies Press.

Nelson, H. E. (1982). *National Adult Reading Test*. NFER-Nelson.

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., Bäckman, L., Hänninen, T., Jula, A., Laatikainen, T., Lindström, J., Mangialasche, F., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T., Tuomilehto, J., … 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. https://doi.org/10.1016/S0140-6736(15)60461-5

Nylund, K. L., Asparouhov, 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: A Multidisciplinary Journal*, *14*(4), 535–569. https://doi.org/10.1080/10705510701575396

Osterrieth, P. A. (1944). Le test de copie d'une figure complexe; contribution à l'étude de la perception et de la mémoire. [Test of copying a complex figure; contribution to the study of perception and memory.]. *Archives de Psychologie*, *30*, 206–356.

Pahor, M., Guralnik, J. M., Ambrosius, W. T., Blair, S., Bonds, D. E., Church, T. S., Espeland, M. A., Fielding, R. A., Gill, T. M., Groessl, E. J., King, A. C., Kritchevsky, S. B., Manini, T. M., McDermott, M. M., Miller, M. E., Newman, A. B., Rejeski, W. J., Sink, K. M., & Williamson, J. D. (2014). Effect of structured physical activity on prevention of major mobility disability in older adults: The LIFE study randomized clinical trial. *JAMA*, *311*(23), 2387–2396. https://doi.org/10.1001/jama.2014.5616

Parisi, J. M., Greene, J. C., Morrow, D. G., & Stine-Morrow, E. A. L. (2007). The Senior Odyssey. *Activities, Adaptation & Aging*, *31*(3), 31–49. https://doi.org/10.1300/J016v31n03_03

Parisi, J. M., Kuo, J., Rebok, G. W., Xue, Q.-L., Fried, L. P., Gruenewald, T. L., Huang, J., Seeman, T. E., Roth, D. L., Tanner, E. K., & Carlson, M. C. (2015). Increases in lifestyle activities as a result of Experience Corps® participation. *Journal of Urban Health*, *92*(1), 55–66. https://doi.org/10.1007/s11524-014-9918-z

Parisi, J. M., Rebok, G. W., Seeman, T. E., Tanner, E. K., Tan, E. J., Fried, L. P., Xue, Q.-L., Frick, K. D., & Carlson, M. C. (2012). Lifestyle activities in sociodemographically at-risk urban, older adults prior to participation in the Baltimore Experience Corps® Trial. *Activities, Adaptation & Aging*, *36*(3), 242–260. https://doi.org/10.1080/01924788.2012.702306

Parra-Medina, D., Wilcox, S., Wilson, D. K., Addy, C. L., Felton, G., & Poston, M. B. (2010). Heart Healthy and Ethnically Relevant (HHER) Lifestyle Trial for improving diet and physical activity in underserved African American women. *Contemporary Clinical Trials*, *31*(1), 92. https://doi.org/10.1016/j.cct.2009.09.006

Pinheiro, J. C., & Chao, E. C. (2006). Efficient Laplacian and Adaptive Gaussian Quadrature Algorithms for Multilevel Generalized Linear Mixed Models. *Journal of Computational and Graphical Statistics*, *15*(1), 58–81. https://doi.org/10.1198/106186006X96962

Podewils, L. J., Guallar, E., Kuller, L. H., Fried, L. P., Lopez, O. L., Carlson, M., & Lyketsos, C. G. (2005). Physical Activity, APOE Genotype, and Dementia Risk: Findings from the Cardiovascular Health Cognition Study. *American Journal of Epidemiology*, *161*(7), 639–651. https://doi.org/10.1093/aje/kwi092

Porta, M. (2008). *A Dictionary of Epidemiology*. Oxford University Press.

Prakash, R. S., Voss, M. W., Erickson, K. I., & Kramer, A. F. (2015). Physical Activity and Cognitive Vitality. *Annual Review of Psychology*, *66*(1), 769–797. https://doi.org/10.1146/annurev-psych-010814-015249

Radloff, L. S. (1977). The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement*, *1*(3), 385–401. https://doi.org/10.1177/014662167700100306

Raji, M. A., Al Snih, S., Ostir, G. V., Markides, K. S., & Ottenbacher, K. J. (2010). Cognitive Status and Future Risk of Frailty in Older Mexican Americans. *The Journals of Gerontology: Series A*, *65A*(11), 1228–1234. https://doi.org/10.1093/gerona/glq121

Raven, J. C. (1956). *Coloured Progressive Matrices*. Western Psychological Services.

Rebok, G. W., Ball, K., Guey, L. T., Jones, R. N., Kim, H.-Y., King, J. W., Marsiske, M., Morris, J. N., Tennstedt, S. L., Unverzagt, F. W., & Willis, S. L. (2014). Ten-year effects of the Advanced Cognitive Training for Independent and Vital Elderly Cognitive Training trial on cognition and everyday functioning in older adults. *Journal of the American Geriatrics Society*, *62*(1), 16–24. https://doi.org/10.1111/jgs.12607

Reese, A. M., Thorpe, R. J., Bell, C. N., Bowie, J. V., & LaVeist, T. A. (2012). The effect of religious service attendance on race differences in depression: Findings from the EHDIC-SWB study. *Journal of Urban Health*, *89*(3), 510–518. https://doi.org/10.1007/s11524-011-9659-1

Reitan, R. M. (1958). Validity of the trial making test as an indicator of organic brain damage. *Perceptual and Motor Skills*, *8*, 271–276. https://doi.org/10.2466/PMS.8.7.271-276

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. https://doi.org/10.1016/j.arr.2013.06.004

Rockwood, K., Andrew, M., & Mitnitski, A. (2007). A Comparison of Two Approaches to Measuring Frailty in Elderly People. *The Journals of Gerontology: Series A*, *62*(7), 738–743. https://doi.org/10.1093/gerona/62.7.738

Rockwood, K., Parhad, I., Hachinski, V., Erkinjuntti, T., Rewcastle, B., Kertesz, A., Eastwood, M. R., & Phillips, S. (1994). Diagnosis of Vascular Dementia: Consortium of Canadian Centres for Clinical Cognitive Research Concensus Statement. *Canadian Journal of Neurological Sciences*, *21*(4), 358–364. https://doi.org/10.1017/S0317167100040968

Rockwood, K., Stadnyk, K., MacKnight, C., McDowell, I., Hébert, R., & Hogan, D. B. (1999). A brief clinical instrument to classify frailty in elderly people. *The Lancet*, *353*(9148), 205–206. https://doi.org/10.1016/S0140-6736(98)04402-X

Rosso, A. L., Auchincloss, A. H., & Michael, Y. L. (2011). *The Urban Built Environment and Mobility in Older Adults: A Comprehensive Review* [Review Article]. Journal of Aging Research; Hindawi. https://doi.org/10.4061/2011/816106

Rosso, A. L., Metti, A. L., Faulkner, K., Redfern, M., Yaffe, K., Launer, L., Elizabeth Shaaban, C., Nadkarni, N. K., & Rosano, C. (2019). Complex Walking Tasks and Risk for Cognitive Decline in High Functioning Older Adults. *Journal of Alzheimer's Disease*, *71*(s1), S65–S73. https://doi.org/10.3233/JAD-181140

Rosso, A. L., Studenski, S. A., Chen, W. G., Aizenstein, H. J., Alexander, N. B., Bennett, D. A., Black, S. E., Camicioli, R., Carlson, M. C., Ferrucci, L., Guralnik, J. M., Hausdorff, J. M., Kaye, J., Launer, L. J., Lipsitz, L. A., Verghese, J., & Rosano, C. (2013). Aging, the Central Nervous System, and mobility. *The Journals of Gerontology: Series A*, *68*(11), 1379–1386. https://doi.org/10.1093/gerona/glt089

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. https://doi.org/10.1177/0898264313482489

Rowe, J. W., & Kahn, R. L. (1997). Successful Aging. *The Gerontologist*, *37*(4), 433–440. https://doi.org/10.1093/geront/37.4.433

Royston, P., & Lambert, P. C. (2011). *Flexible parametric survival analysis using Stata: Beyond the Cox model*. Stata Press.

Sajeev, G., Weuve, J., Jackson, J. W., VanderWeele, T. J., Bennett, D. A., Grodstein, F., & Blacker, D. (2016). Late-life cognitive activity and dementia: A systematic review and bias analysis. *Epidemiology*, *27*(5), 732–742. https://doi.org/10.1097/EDE.0000000000000513

Salthouse, T. A. (2006). Mental exercise and mental aging: Evaluating the validity of the "use it or lose it" hypothesis. *Perspectives on Psychological Science*, *1*(1), 68–87. https://doi.org/10.1111/j.1745-6916.2006.00005.x

Salthouse, T. A. (2016). *Theoretical Perspectives on Cognitive Aging*. Psychology Press.

Saunders, D. H., Sanderson, M., Hayes, S., Kilrane, M., Greig, C. A., Brazzelli, M., & Mead, G. E. (2016). Physical fitness training for stroke patients. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD003316.pub6

Saxton, J, Lopez, O. L., Ratcliff, G., Dulberg, C., Fried, L. P., Carlson, M. C., Newman, A. B., & Kuller, L. (2004). Preclinical Alzheimer disease: Neuropsychological test performance 1.5 to 8 years prior to onset. *Neurology*, 8.

Saxton, Judith, Ratcliff, G., Munro, C. A., Coffey, E. C., Becker, J. T., Fried, L., & Kuller, L. (2000). Normative Data on the Boston Naming Test and Two Equivalent 30-Item Short Forms. *The Clinical Neuropsychologist*, *14*(4), 526–534. https://doi.org/10.1076/clin.14.4.526.7204

Scarmeas, N., Levy, G., Tang, M.-X., Manly, J., & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's Disease. *Neurology*, *57*(12), 2236–2242. https://doi.org/10.1212/WNL.57.12.2236

Schaie, K. W., & Willis, S. L. (2010). The Seattle Longitudinal Study of adult cognitive development. *ISSBD Bulletin*, *57*(1), 24–29.

Schaie, K. W., Willis, S. L., & Caskie, G. I. L. (2004). The Seattle Longitudinal Study: Relationship between personality and cognition. *Aging, Neuropsychology, and Cognition*, *11*(2–3), 304–324. https://doi.org/10.1080/13825580490511134

Schinka, J. A., Mcbride, A., Vanderploeg, R. D., Tennyson, K., Borenstein, A. R., & Mortimer, J. A. (2005). Florida Cognitive Activities Scale: Initial development and validation. *Journal of the International Neuropsychological Society*, *11*(1), 108–116. https://doi.org/10.1017/S1355617705050125

Schooler, C. (1984). Psychological effects of complex environments during the life span: A review and theory. *Intelligence*, *8*(4), 259–281. https://doi.org/10.1016/0160-2896(84)90011-4

Schreiber, S., Vogel, J., Schwimmer, H. D., Marks, S. M., Schreiber, F., & Jagust, W. (2016). Impact of lifestyle dimensions on brain pathology and cognition. *Neurobiology of Aging*, *40*, 164–172. https://doi.org/10.1016/j.neurobiolaging.2016.01.012

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology*, *4*, 1–32.

Sliwinski, M. J., Mogle, J. A., Hyun, J., Munoz, E., Smyth, J. M., & Lipton, R. B. (2018). Reliability and Validity of Ambulatory Cognitive Assessments. *Assessment*, *25*(1), 14–30. https://doi.org/10.1177/1073191116643164

Small, B. J., Hughes, T. F., Hultsch, D. F., & Dixon, R. A. (2013). Lifestyle activities and late-life changes in cognitive performance. In Y. Stern (Ed.), *Cognitive Reserve: Theory and Applications* (pp. 187–200). Psychology Press.

Smith, J., Ryan, L. H., Queen, T. L., Becker, S., & Gonzalez, R. (2014). Snapshots of mixtures of affective experiences in a day: Findings from the Health and Retirement Study. *Journal of Population Ageing*, *7*(1), 55–79. https://doi.org/10.1007/s12062-014-9093-8

Snitz, B. E., O'Meara, E. S., Carlson, M. C., Arnold, A. M., Ives, D. G., Rapp, S. R., Saxton, J., Lopez, O. L., Dunn, L. O., Sink, K. M., & DeKosky, S. T. (2009). Ginkgo biloba for Preventing Cognitive Decline in Older Adults: A Randomized Trial. *JAMA*, *302*(24), 2663–2670. https://doi.org/10.1001/jama.2009.1913

Snitz, B. E., Saxton, J., Lopez, O. L., Ives, D. G., Dunn, L. O., Rapp, S. R., Carlson, M. C., Fitzpatrick, A. L., & DeKosky, S. T. (2009). Identifying mild cognitive impairment at baseline in the Ginkgo Evaluation of Memory (GEM) study. *Aging & Mental Health*, *13*(2), 171–182. https://doi.org/10.1080/13607860802380656

Snyder, H. M., Corriveau, R. A., Craft, S., Faber, J. E., Greenberg, S., Knopman, D., Lamb, B. T., Montine, T., Nedergaard, M., Schaffer, C. B., Schneider, J. A., Wellington, C., Wilcock, D. M.,

Zipfel, G. J., Zlokovic, B., Bain, L. J., Bosetti, F., Galis, Z. S., Koroshetz, W., & Carrillo, M. C. (2015). Vascular contributions to cognitive impairment and dementia including Alzheimer's Disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *11*(6), 710–717. https://doi.org/10.1016/j.jalz.2014.10.008

Spreen, O., & Strauss, E. A. (1998). *A Compendium of Neuropsychological Tests*. Oxford University Press.

Steptoe, A., & Wardle, J. (2011). Positive affect measured using ecological momentary assessment and survival in older men and women. *Proceedings of the National Academy of Sciences*, *108*(45), 18244–18248. https://doi.org/10.1073/pnas.1110892108

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*(3), 448–460. https://doi.org/10.1017/S1355617702813248

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Stine-Morrow, E. A. L., Parisi, J. M., Morrow, D. G., Greene, J., & Park, D. C. (2007). An Engagement Model of Cognitive Optimization Through Adulthood. *The Journals of Gerontology: Series B*, *62*(Special_Issue_1), 62–69. https://doi.org/10.1093/geronb/62.special_issue_1.62

Stricker, J. L., Brown, G. G., Wixted, J., Baldo, J. V., & Delis, D. C. (2002). New semantic and serial clustering indices for the California Verbal Learning Test–Second Edition: Background, rationale, and formulae. *Journal of the International Neuropsychological Society*, *8*(3), 425–435. https://doi.org/10.1017/S1355617702813224

Ströhle, A., Schmidt, D. K., Schultz, F., Fricke, N., Staden, T., Hellweg, R., Priller, J., Rapp, M. A., & Rieckmann, N. (2015). Drug and Exercise Treatment of Alzheimer Disease and Mild Cognitive Impairment: A Systematic Review and Meta-Analysis of Effects on Cognition in Randomized Controlled Trials. *The American Journal of Geriatric Psychiatry*, *23*(12), 1234–1249. https://doi.org/10.1016/j.jagp.2015.07.007

Studenski, S., Perera, S., Patel, K., Rosano, C., Faulkner, K., Inzitari, M., Brach, J., Chandler, J., Cawthon, 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. *JAMA*, *305*(1), 50–58. https://doi.org/10.1001/jama.2010.1923

Teng, E. L., & Chui, H. C. (1987). The Modified Mini-Mental State (3MS) examination. *The Journal of Clinical Psychiatry*, *48*(8), 314–318.

Trenerry, M. R., Crosson, B., DeBoe, J., & Lever, W. R. (1989). *Stroop Neuropsychological Screening Test*. Psychological Assessment Resources.

Tzuang, M., Owusu, J. T., Spira, A. P., Albert, M. S., & Rebok, G. W. (2018). Cognitive training for ethnic minority older adults in the United States: A review. *The Gerontologist*, *58*(5), e311–e324. https://doi.org/10.1093/geront/gnw260

Unger, J. B., Johnson, C. A., & Marks, G. (1997). Functional decline in the elderly: Evidence for direct and stress-buffering protective effects of social interactions and physical activity,. *Annals of Behavioral Medicine*, *19*(2), 152–160. https://doi.org/10.1007/BF02883332

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. *The Journals of Gerontology: Series A*, *71*(11), 1451–1458. https://doi.org/10.1093/gerona/glw080

Varma, V. R., Tan, E. J., Gross, A. L., Harris, G., Romani, W., Fried, L. P., Rebok, G. W., & Carlson, M. C. (2016). Effect of community volunteering on physical activity: A randomized controlled trial. *American Journal of Preventive Medicine*, *50*(1), 106–110. https://doi.org/10.1016/j.amepre.2015.06.015

Varma, V. R., Tan, E. J., Wang, T., Xue, Q.-L., Fried, L. P., Seplaki, C. L., King, A. C., Seeman, T. E., Rebok, G. W., & Carlson, M. C. (2014). Low-Intensity Walking Activity Is Associated With Better Health. *Journal of Applied Gerontology*, *33*(7), 870–887. https://doi.org/10.1177/0733464813512896

Verbrugge, L. M., Gruber-Baldini, A. L., & Fozard, J. L. (1996). Age differences and age changes in activities: Baltimore Longitudinal Study of Aging. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *51B*(1), S30–S41. https://doi.org/10.1093/geronb/51B.1.S30

Verghese, J., LeValley, A., Hall, C. B., Katz, M. J., Ambrose, A. F., & Lipton, R. B. (2006). Epidemiology of gait disorders in community-residing older adults. *Journal of the American Geriatrics Society*, *54*(2), 255–261. https://doi.org/10.1111/j.1532-5415.2005.00580.x

Verghese, J., Lipton, R. B., Hall, C. B., Kuslansky, G., Katz, M. J., & Buschke, H. (2002). Abnormality of Gait as a Predictor of Non-Alzheimer's Dementia. *New England Journal of Medicine*, *347*(22), 1761–1768. https://doi.org/10.1056/NEJMoa020441

Verghese, J., Lipton, R. B., Katz, M. J., Hall, C. B., Derby, C. A., Kuslansky, G., Ambrose, A. F., Sliwinski, M., & Buschke, H. (2003a). Leisure activities and the risk of dementia in the elderly. *New England Journal of Medicine*, *348*(25), 2508–2516. https://doi.org/10.1056/NEJMoa022252

Verghese, J., Lipton, R. B., Katz, M. J., Hall, C. B., Derby, C. A., Kuslansky, G., Ambrose, A. F., Sliwinski, M., & Buschke, H. (2003b). Leisure activities and the risk of dementia in the elderly. *New England Journal of Medicine*, *348*(25), 2508–2516. https://doi.org/10.1056/NEJMoa022252

Verhaeghen, P., & Salthouse, T. A. (1997). Meta-analyses of age-cognition relations in adulthood: Estimates of linear and nonlinear age effects and structural models. *Psychological Bulletin*, *122*(3), 231–249.

Vermunt, J. K. (2010). Latent class modeling with covariates: Two improved three-step approaches. *Political Analysis*, *18*(04), 450–469. https://doi.org/10.1093/pan/mpq025

Voss, M. W., Carr, L. J., Clark, R., & Weng, T. (2014). Revenge of the "sit" II: Does lifestyle impact neuronal and cognitive health through distinct mechanisms associated with sedentary behavior and physical activity? *Mental Health and Physical Activity*, *7*(1), 9–24. https://doi.org/10.1016/j.mhpa.2014.01.001

Voss, M. W., Nagamatsu, L. S., Liu-Ambrose, T., & Kramer, A. F. (2011). Exercise, brain, and cognition across the life span. *Journal of Applied Physiology*, *111*(5), 1505–1513. https://doi.org/10.1152/japplphysiol.00210.2011

Walston, J. D., & Bandeen-Roche, K. (2015). Frailty: A tale of two concepts. *BMC Medicine*, *13*(1), 185. https://doi.org/10.1186/s12916-015-0420-6

Wechsler, D. (1981). *Wechsler Adult Intelligence Scale – Revised*. Psychological Corporation.

Wechsler, D. (1987). *Wechsler memory scale-revised*. Psychological Corporation.

Wilson, R. S., Bennett, D. A., Beckett, L. A., Morris, M. C., Gilley, D. W., Bienias, J. L., Scherr, P. A., & Evans, D. A. (1999). Cognitive activity in older persons from a geographically defined population. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *54*(3), P155-160.

Wilson, R. S., Scherr, P. A., Schneider, J. A., Tang, Y., & Bennett, D. A. (2007). Relation of cognitive activity to risk of developing Alzheimer disease. *Neurology*, *69*(20), 1911–1920. https://doi.org/10.1212/01.wnl.0000271087.67782.cb

Wilson, Robert S, Barnes, L. L., Krueger, K. R., Hoganson, G., Bienias, J. L., & Bennett, D. A. (2005). Early and late life cognitive activity and cognitive systems in old age. *Journal of the International Neuropsychological Society*, *11*, 400–407. https://doi.org/10.10170S1355617705050459

Wilson, Robert S., & Bennett, D. A. (2003). Cognitive Activity and Risk of Alzheimer's Disease. *Current Directions in Psychological Science*, *12*(3), 87–91. https://doi.org/10.1111/1467-8721.01236

Wilson, Robert S., Leon, C. F. M. de, Barnes, L. L., Schneider, J. A., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2002). Participation in cognitively stimulating activities and risk of incident Alzheimer Disease. *JAMA*, *287*(6), 742–748. https://doi.org/10.1001/jama.287.6.742

Wu, Y., Beiser, A. S., Breteler, M. M. B., Fratiglioni, L., Helmer, C., Hendrie, H. C., Honda, H., Ikram, M. A., Langa, K. M., Lobo, A., Matthews, F., Ohara, T., Peres, K., Qiu, C., Seshadri, S., Sjolund, B. M., Skoog, I., & Brayne, C. (2017). The changing prevalence and incidence of dementia over time—Current evidence. *Nature Reviews Neurology*, *13*(6), 327.

Xue, Q.-L. (2011). The Frailty Syndrome: Definition and Natural History. *Clinics in Geriatric Medicine*, *27*(1), 1–15. https://doi.org/10.1016/j.cger.2010.08.009

Xue, Q.-L., Bandeen-Roche, K., Varadhan, R., Zhou, J., & Fried, L. P. (2008). Initial Manifestations of Frailty Criteria and the Development of Frailty Phenotype in the Women's Health and Aging Study II. *The Journals of Gerontology: Series A*, *63*(9), 984–990. https://doi.org/10.1093/gerona/63.9.984

Xue, Q.-L., Buta, B., Ma, L., Ge, M., & Carlson, M. (2019). Integrating Frailty and Cognitive Phenotypes: Why, How, Now What? *Current Geriatrics Reports*, *8*(2), 97–106. https://doi.org/10.1007/s13670-019-0279-z

Xue, Q.-L., Fried, L. P., Glass, T. A., Laffan, A., & Chaves, P. H. M. (2008). Life-Space Constriction, Development of Frailty, and the Competing Risk of MortalityThe Women's Health and Aging Study I. *American Journal of Epidemiology*, *167*(2), 240–248. https://doi.org/10.1093/aje/kwm270

Zahodne, L. B., Manly, J. J., MacKay-Brandt, A., & Stern, Y. (2013). Cognitive Declines Precede and Predict Functional Declines in Aging and Alzheimer's Disease. *PLoS ONE*, *8*(9). https://doi.org/10.1371/journal.pone.0073645

Zahodne, L. B., Sol, K., & Kraal, Z. (2017). Psychosocial pathways to racial/ethnic inequalities in late-life memory trajectories. *The Journals of Gerontology: Series B*. https://doi.org/10.1093/geronb/gbx113

Zweig, M. H., & Campbell, G. (1993). Receiver-operating characteristic (ROC) plots: A fundamental evaluation tool in clinical medicine. *Clinical Chemistry*, *39*(4), 561–577. https://doi.org/10.1093/clinchem/39.4.561

CURRICULUM VITAE

Kyle D. Moored
Doctoral Candidate

PERSONAL DATA

Johns Hopkins Center on Aging and Health
Johns Hopkins Bloomberg School of Public Health
Department of Mental Health
624 N. Broadway, Hampton House Rm. 897, Baltimore, MD 21205
Email: kmoored1@jhu.edu

EDUCATION

09/2016 – Present	Doctoral Candidate, Mental Health Johns Hopkins Bloomberg School of Public Health Advisor: Michelle Carlson, Ph.D.
09/2010 – 05/2014	B.S., Psychology, With Highest Distinction University of Michigan, Ann Arbor, MI Advisors: Patricia Reuter-Lorenz, Ph.D. & Eric Kim, Ph.D.

PROFESSIONAL EXPERIENCE

09/2016 – Present	Graduate Research Assistant, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health
10/2014 – 07/2016	Project Coordinator, Cognitive and Affective Neuropsychology Laboratory, University of Michigan Department of Psychology Advisor: Patricia Reuter-Lorenz, Ph.D.
12/2012 – 05/2014	Research Assistant, Institute for Social Research: Psychosocial Aging Group, University of Michigan Advisor: Eric Kim, Ph.D.
05/2012 – 05/2013	Research Assistant, Cognitive and Affective Neuropsychology Laboratory, University of Michigan Department of Psychology Advisor: Patricia Reuter-Lorenz, Ph.D.

GRANTS AND AWARDS

10/2019	Travel award from the Department of Mental Health at JHSPH for Gerontological Society of America Conference in November 2019 ($600)
04/2019	Paul V. Lemkau Scholarship Fund Award ($5116)
08/2018	Invited and funded participant for the "Workshops Modeling Dementia Progression" for the Integrative Analysis of Longitudinal

	Studies of Aging and Dementia (IALSA) Network in Amsterdam, Netherlands
09/2016 – Present	Pre-doctoral Fellow in the Epidemiology and Biostatistics of Aging Training Program (T32AG000247), Johns Hopkins Center on Aging and Health
05/2014	Graduated with Highest Distinction
04/2014	Phi Beta Kappa Honor Society
09/2013	George (William Hamby and Libbie B.) Merit Scholarship, $5000
2011 – 2014	James B. Angell Academic Scholar, University of Michigan
2010 – 2013	University of Michigan Honors

PUBLICATIONS

Manuscripts

In Progress

Moored, K. D., Bandeen-Roche, K., Snitz, B. E., Fitzpatrick, A. L., DeKosky, S. T., Williamson, J. D., Carlson, M. C. (in preparation). Risk of Dementia differs across Lifestyle Complexity Subgroups: A Latent Class and Time to Event Analysis in Community-Dwelling Older Adults.

Moored, K. D., Cooke, K. A., Iordan, A. D., Katz, B., Frank, C., Buschkuehl, M. Jaeggi S. M., Jonides J., Polk T. A., Reuter-Lorenz, P. A. (in preparation). Predictors of Verbal Working Memory Plasticity in Younger and Older Adults: Dissociating Early and Late Learning Effects.

Thurl, J., **Moored, K. D.,** Tormohlen, K. N. (in preparation). Predictors of Compliance with Ecological Momentary Assessment Measures of Smoking Behaviors.

Published

Iordan, A. D., Cooke, K. A., **Moored, K. D.,** Katz, B., Buschkuehl, M., Jaeggi, S. M., ... & Reuter-Lorenz, P. A. (in press). Neural Correlates of Working Memory Training: Evidence for Plasticity in Older Adults. *NeuroImage.*

Yasar, S., **Moored, K. D.,** Adam, A., Zabel, F., Chuang, Y. F., Varma, V. R., & Carlson, M. C. (2020). Angiotensin II Blood Levels Are Associated with Smaller Hippocampal and Cortical Volumes in Cognitively Normal Older Adults. *Journal of Alzheimer's Disease*, (Preprint), 1-9.

Moored, K. D., Chan, T., Varma, V. R., Chuang, Y., Parisi, J. M., Carlson, M. C. (2018). Engagement in Enriching Early Life Activities is Associated with Larger Hippocampal and Amygdala Volumes in Community-Dwelling Older Adults. *Journals of Gerontology Series B: Psychological Sciences.*

Chan, T., Parisi, J. M., **Moored, K. D.,** Carlson, M. C. (2018). Variety of early life enriching activities predicts late life cognition in community-dwelling African Americans. *Journal of Gerontology Series B: Psychological Sciences.*

Iordan, A. D., Cooke, K. A., **Moored, K. D.,** Katz, B., Buschkuehl, M. Jaeggi S. M., Jonides J., Peltier S. J., Polk T. A., & Reuter-Lorenz P. A. (2018). Aging and network properties: Stability over time and links with learning during working memory training. *Frontiers in Aging Neuroscience, 9*, 419.

Kim, E. S., **Moored, K. D.,** Giasson H. L., & Smith, J. (2014). Satisfaction with aging and use of preventive health services. *Preventive Medicine, 69*, 176-180.

Book Chapters

Carlson, M. C., **Moored, K. D.,** Rebok, G. W., Eaton, W. W. (2019). Public Mental health and the Brain Across the Lifespan. In W. W. Eaton & M.D. Fallin (Eds.), *Public Mental Health (second edition)*. Oxford, UK: Oxford University Press

PRESENTATIONS/ABSTRACTS

Scientific Meetings

Moored, K. D., Parisi, J. M., Snitz, B. E., DeKosky, S. T., Williamson, J. D., Fitzpatrick, A. L., Carlson, M. C. (accepted). *Examining Risk of Dementia in Lifestyle Engagement Subgroups of Community-Dwelling Older Adults: A Latent Class Approach.* Talk to be presented at the Alzheimer's Association International Conference, Amsterdam, Netherlands, July 29, 2020.

Moored, K. D., Parisi, J. M., Carlson, M. C. (2020). *Examining Risk of Incident Dementia and Cognitive Trajectories in Lifestyle Engagement Subgroups of Community-Dwelling Older Adults: A Latent Class Approach.* Poster presentation at Cognitive Aging Conference, Atlanta, GA, April 19, 2020. (Conference canceled)

Moored K., Parisi J. M., Carlson M. (2019). *Examining Whether Lifestyle Activity Patterns Predict Dementia Incidence Among Community-Dwelling Older Adults.* Talk presented at the annual meeting of the Gerontological Society of America, Austin, TX, November 17, 2019.

Iordan, A. D., Cooke, K. A., **Moored, K. D.,** Katz, B., Buschkuehl, M., Jaeggi, S. M., Polk, T. A., Peltier, S. J., Jonides, J., & Reuter-Lorenz, P. A. (2019). *Aging and Working Memory Training: Testing the Compensation Related Utilization of Neural Circuits Hypothesis*

(CRUNCH). Talk presented by Dr. Alexandru Iordan at the 2019 Society for Neuroscience Meeting, Chicago, IL.

Yasar, S., **Moored, K. D.,** Zabel, F., Chuang, Y., Varma, V. R., & Carlson, M. C. (2019). *Angiotensin II and Brain Volumes in Older Adults in the Baltimore Experience Corps Trial (BECT) Brain Health Study.* Poster presented by Dr. Sevil Yasar at the 2019 Alzheimer's Association International Conference, Los Angeles, CA.

Haaksma, M. L., Banning, L., …, **Moored, K. D.,** … , Hofer, S., Melis, R., Muniz-Terrera, G. (2019). Cognitive progression of dementia after diagnosis: a coordinated analysis of 12 cohorts. Talk presented by Dr. Miriam Haaksma at the International Association of Gerontology and Geriatrics European Region (IAGG-ER) Congress 2019.

Crane, B., **Moored, K. D.,** Adam, A., Chan, T., Morreale, M., Notti, M., Zabel, F., Carlson, M. C. (2019). *Bandit the Dolphin: Feasibility Study of an Immersive 3-D Reality Game to Promote Executive Function and Community Mobility in Aging Adults*. Poster presented by Breanna Crane at the 2019 Aging Research Showcase at Johns Hopkins Bloomberg School of Public Health.

Iordan, A. D., Cooke, K. A., **Moored, K. D.,** Katz, B., Buschkuehl, M., Jaeggi, S. M., Jonides, J., Peltier, S. J., Polk, T. A., & Reuter-Lorenz, P. A. (2019). *The Compensation Related Utilization of Neural Circuits Hypothesis (CRUNCH): Evidence that Working Memory Training Benefits Younger and Older Adults.* Talk presented by Dr. Alexandru Iordan at the 2019 Dallas Aging and Cognition Conference, Dallas, TX.

Moored, K. D., Leroux, A., Varma, V. R., Chuang, Y., Parisi, J. M., Carlson, M. C. (2018). *Daily Step Activity Metrics as predictors of Prefrontal Cortical Volume and Executive Functioning in Older Adults.* Poster presented at the 2018 meeting Gerontological Society of America, Boston, MA

Iordan, A. D., Cooke, K. A., **Moored, K. D.,** Katz, B., Buschkuehl, M., Jaeggi, S. M., Polk, T. A., Peltier, S. J., Jonides, J., & Reuter-Lorenz, P. A. (2018). *Working memory training reduces neural recruitment in older adults: Support for the Compensation Related Utilization of Neural Circuits Hypothesis.* Poster presented by Dr. Alexandru Iordan at the 2018 Psychonomics Society Conference, New Orleans, LA.

Iordan, A. D., Cooke, K. A., **Moored, K. D.,** Katz, B., Rajen, S., Buschkuehl, M., Jaeggi, S. M., Peltier, S. J., Polk, T. A., Jonides, J., & Reuter-Lorenz, P. A. (2018). *Behavioral and Brain-Imaging Predictors of Working Memory Plasticity in Younger and Older Adults.* Poster presented by Dr. Alexandru Iordan at the 2018 Cognitive Neuroscience Society Conference, Dallas, TX.

Moored, K. D., Chan, T., Varma, V. R., Chuang, Y., Parisi, J. M., Carlson, M. C. (2018). *Early life enrichment predicts hippocampal and amygdala volumes in older adulthood.* Poster presented at the 2018 annual meeting of the Cognitive Aging Conference, Atlanta, GA.

Chan, T., Parisi, J. M., **Moored, K. D.,** Carlson, M. C. (2018). *Enriching early life activities to build cognitive reserves and combat health disparities.* Poster presented by Dr. Thomas Chan at the annual meeting of the Cognitive Aging Conference, Atlanta, GA.

Moored, K. D., Cooke, K. A., Katz, B., Buschkuehl, M., Jaeggi, S. M., Peltier S. J., Polk, T. A., Jonides, J., Reuter-Lorenz, P. A. (2017). Predictors of verbal working memory plasticity in younger and older adults. Poster presented at the 2017 Dallas Aging and Cognition Conference, Dallas, TX.

Cooke, K. A., Iordan, A. D., **Moored, K. D.,** Katz, B., Buschkuehl, M., Jaeggi, S. M., Polk, T. A., Peltier S. J., Jonides, J., Reuter-Lorenz, P. A. (2017). Evaluating CRUNCH: Age differences in the neural response to varying working memory demand. Poster presented by Katherine Cooke at annual meeting of the Dallas Aging and Cognition Conference, Dallas, TX.

Cooke K. A., Katz, B., **Moored K. D.,** Buschkuehl, M., Jaeggi S. M., Peltier S. J., Polk T. A., Jonides J., & Reuter-Lorenz P. A. (2015). Practice based malleability of verbal working memory performance. Poster presented by Katherine Cooke at annual meeting of the Psychonomics Society, Chicago, IL.

Invited Talks

Crane, B., **Moored, K. D.** (2020). *21st Century Tools for Cognitive Assessment and Game-Based Interventions in Older Populations.* Served as co-facilitator and co-presenter for interactive session for Department of Mental Health Seminar Series.

Moored, K. D. (2020). *Defining Lifestyle Activity Engagement in Later Life: Frequency, Variety, Types, or All of the Above?* Served as facilitator and presenter for February meeting of the "Issue is…" Seminar Series at the Johns Hopkins School of Nursing.

Moored, K. D. (2019). *Brain Plasticity and Interventions to Prevent Dementia.* Guest lecture for the course "Brain and Behavior in Mental Disorders" in the Department of Mental Health.

Moored, K. D. (2018). *What to do? Treatment and Prevention Strategies for Mental Health Disorders.* Guest lecture for the course "Public Mental Health" in the Department of Mental Health.

Moored, K. D. (2018). *Brain Plasticity and Interventions to Prevent Dementia.* Guest lecture for the course "Brain and Behavior in Mental Disorders" in the Department of Mental Health.

Moored, K. D. (2017). *Early engagement is associated with later life brain volumes.* Talk for Department of Mental Health Seminar Series.

TEACHING/MENTORING EXPERIENCE

10/2019 – 01/2020 **Teaching Assistant,** Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Course Title: "Psychiatric Epidemiology"
Developed course syllabus and reading list in conjunction with instructors and co-TA, graded and provided individualized feedback on assignments and final exam, communicated with students. Mentored doctoral students on their independent public data analysis project. Received 71% "excellent" and 29% "good" ratings from students (0% fair/poor).

03/2019 – 05/2019 **Teaching Assistant,** Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Course Title: "Brain and Behavior in Mental Disorders"
Developed course syllabus and reading list in conjunction with instructor, graded and provided individualized feedback on assignments and projects, proctored final exam, communicated with students. Developed rubrics for thought paper and presentation assignments based on feedback from students in the course last year. Received 96% "excellent" and 4% "good" ratings from students (0% fair/poor).

09/2018 – 11/2018 **Teaching Assistant,** Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Course Title: "Public Mental Health"
Developed course syllabus, reading list, and lecture slides in conjunction with instructor, graded and provided individualized feedback on assignments and projects, communicated with students. Received 84% "excellent" and 14% "good" ratings from students.

03/2018 – 05/2018 **Teaching Assistant,** Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Course Title: "Brain and Behavior in Mental Disorders"
Developed course syllabus and reading list in conjunction with instructor, graded and provided individualized feedback on assignments and projects, proctored final exam, communicated with students. Received 91% "excellent" and 9% "good" ratings from students (0% fair/poor).

09/2017 – Present **Peer Mentor,** Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Advised eight Master's students on courses and program requirements; acted as liaison between mentees and department faculty and staff.

PROFESSIONAL ACTIVITIES

JHSPH Wellness and Quality of Life Committee, Student Representative
Mental Health Student Group, President
Gerontological Society of America, Member
Brain Health Study Working Group
Latent Variable Modeling Working Group
Epidemiology of Aging Journal Club

EDITORIAL ACTIVITIES

Neurobiology of Aging (student reviewer, primary reviewer: Dr. Michelle Carlson)
Journal of Gerontology Series A: Medical Sciences (student reviewer, primary reviewer: Dr. Michelle Carlson)
Journal of Gerontology Series B: Psychological Sciences (student reviewer, primary reviewer: Dr. Michelle Carlson)
International Journal of Environmental Research and Public Health (primary reviewer)

PROFESSIONAL AND COMMUNITY SERVICE

08/2016 – Present **Graduate Student Researcher,** "Stimulation with Intricate Movements" (SWIM) Pilot Study, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Developed study recruitment and assessment protocol for a motion-based, immersive video game intervention. Co-developed tablet-based cognitive testing battery for baseline and follow-up evaluations. Facilitated integration of the intervention within BrightView Retirement Community in Catonsville, MD. Communicated with and administered study protocol to participants. Developed an active control group intervention (i.e., arm bike protocol) for future use in a randomized trial.

06/2019 – Present **Student Representative**, Johns Hopkins Bloomberg School of Public Health Wellness and Quality of Life Committee

Served as student-group liaison to connect the committee with existing student intiatives. Served on "Destress" subcommittee creating wellness promotion materials and recruiting wellness event facilitators for the kickoff event and ongoing destress initiatives (e.g., mindfulness and yoga exercises).

08/2018 – 08/2019 **President,** Mental Health Student Group, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Recruited and managed core team of five students to plan professional development, networking, and wellness events for students in the Department. Managed the annual budget (~$2000). Organized and facilitated student-led seminar talks during the Department's Wednesday noon seminar series.

10/2018 – 12/2018 **Seminar Series Leader,** Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Seminar Series Title: "Cognitive Aging"
Initiated and co-organized a three-session departmental seminar series that included student-led and guest faculty lectures spanning diverse topics within cognitive aging (e.g., prevention, health disparities, etc.). Developed a core planning team including both students and faculty, drafted invitation letters for guest faculty speakers, and facilitated seminars and post-session networking periods.

05/2017 – 06/2018 **Volunteer Scribe,** Center for Innovative Care in Aging Summer Research Institute on Behavioral Interventions

Volunteered starting for the 2017 workshop. Invited to return as volunteer in 2018. Transcribed dialogue from group workshops, including attendee descriptions of their proposed interventions and methodological advice provided by workshop directors. Synthesized transcribed material and provided summaries of key points to workshop attendees.

09/2013 – 05/2014 **Tutor,** American Reads, University of Michigan Ginsburg Center

Tutored several first-grade students on reading and language skills. Planned and administered individualized lesson plans and activities for each session.

09/2013 – 05/2014 **Volunteer Recreation Staff,** Glacier Hills Retirement Community, Ann Arbor, MI

Facilitated group activities for residents that promoted physical and mental wellness.

TECHNICAL SKILLS
Proficient in E-Prime
Proficient in Qualtrics survey application
Proficient in MPlus, STATA and SPSS
Proficient with administering and scoring standardized neuropsychological batteries
Experience with R
Experience with SPM8, FSL, FreeSurfer, and MATLAB
Experience with Python