Longitudinal Patterns of Cognitive State Changes and their Predictors in Older Adults

by

Maryam Iraniparast

A thesis
presented to the University of Waterloo
in fulfillment of the
thesis requirement for the degree of
Doctor of Philosophy
in
Public Health and Health Systems

Waterloo, Ontario, Canada, 2020

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Examining Committee Membership

The following served on the Examining Committee for this thesis. The decision of the Examining Committee is by majority vote.

External Examiner	Roger A. Dixon, PhD Professor, Canada Research Chair, Director, Victoria Longitudinal Study Department of Psychology University of Alberta
Co-Supervisors	Suzanne L Tyas, PhD Associate Professor School of Public Health and Health Systems University of Waterloo
	Joel A Dubin, PhD Associate Professor Department of Statistics and Actuarial Science and School of Public Health and Health Systems University of Waterloo
Internal Members	Colleen J Maxwell, PhD Professor, University Research Chair School of Pharmacy and School of Public Health and Health Systems University of Waterloo
	Philip St. John, MD, MPH, FRPCP Associate Professor Section of Geriatrics, Department of Internal Medicine, and the Centre on Aging, Max Rady College of Medicine University of Manitoba
Internal/External Member	Cecilia A Cotton, PhD Associate Professor, Department of Statistics and Actuarial Science University of Waterloo

Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

This thesis consists in part of three manuscripts that will be submitted for publication. Exceptions to sole authorship include Chapters 4, 5, and 6.

As lead author of these three chapters, I was responsible for developing the research questions, conducting background research, identifying the analytic approaches, conducting the statistical analyses, interpreting the results, and writing the initial drafts of the manuscripts. My co-authors provided guidance during each step of the research and provided feedback on draft manuscripts.

Under Dr. Tyas's and Dr. Dubin's supervision, I also prepared the remaining chapters in this thesis, which were not written for publication.

Abstract

Older adults experience diverse patterns of cognitive state changes, including progression to dementia, that depend on genetic and non-genetic factors. With population aging, the global prevalence of dementia is rising. Given limited treatment success, research focusing on patterns of cognitive state changes and their predictors provides information for older adults and opens windows to develop interventions for preventing or delaying the onset of dementia.

This dissertation is based on analyzing secondary data from the Nun Study, a longitudinal study of aging and cognition. The first aim of this dissertation was to identify patterns of changes over time in cognitive states among older adults using a clinically-driven approach and a statistical modeling method, and to compare the patterns identified using these two methods. The second aim was to test and quantify how academic achievement—educational attainment and academic performance in high school—is associated with cognitive state changes and contributes to cognitive reserve. The third aim was to test the potential antagonistic pleiotropy effect of the gene apolipoprotein E (*APOE*) on cognition.

To identify the patterns of cognitive state changes (Aim 1), homogeneous trajectories were grouped together using two different approaches: 1) a clinically-driven approach, and 2) a statistical modeling approach, latent class mixed-effects modeling (lcmm). Using the clinically-driven approach, seven patterns were identified based on whether individuals experienced stable or non-stable trajectories and among non-stable trajectories, whether they experienced a reverse transition to an improved cognitive state, whether they developed dementia or both. These seven trajectories ranged from stable normal cognition to stable dementia. These patterns were preferred to the four classes identified using latent class mixed-effects modeling. This preference was based on the higher level of detail in trajectories captured by the clinically-driven approach compared to the latent classes identified using the lcmm approach. These details include distinguishing between trajectories with and without cognitive improvement, and with and without progression to dementia. The patterns of cognitive state changes based on the clinically-driven approach were then used as the cognitive outcomes to address the two additional aims, with stable dementia used as the reference category.

Using multinomial logistic bias reduction regression, the potential presence of cognitive reserve among individuals with higher academic achievement was tested (Aim 2). Adjusting for age and *APOE*, higher educational attainment (i.e., a graduate degree) was associated with higher odds of experiencing three healthier patterns of cognitive state changes. Higher overall academic performance was significantly associated with experiencing stable cognitive impairment or cognitive impairment without dementia; this effect was mostly due to higher performance in algebra rather than performance in English, Latin, or geometry courses. Higher academic achievement, as evidenced by educational attainment or performance in high school courses, was thus associated with cognitive reserve through experiencing healthier patterns of cognitive trajectories versus experiencing stable dementia.

To test the potential antagonistic pleiotropy effect of *APOE* on cognition, the effect of *APOE*-ε4 on both early- and late-life cognition was investigated (Aim 3). In addition, the potential modifying effect of higher education among *APOE*-ε4 carriers was tested. *APOE*-ε4 was not significantly associated with an early-life measure of cognition (educational attainment); however, among individuals with lower education, *APOE*-ε4 was associated with experiencing the most impaired cognitive pattern (stable dementia) in late life. This research did not support the antagonistic pleiotropy hypothesis for *APOE*; however, it did support the scaffolding theory of aging and cognition. Higher educational attainment among *APOE*-ε4 carriers compensated for the detrimental effects of *APOE*-ε4 on late-life cognition to the extent that *APOE*-ε4 carriers with high educational attainment (a graduate degree) showed cognitive aging patterns similar to *APOE*-ε4 non-carriers. This modifying effect of higher education on the association between *APOE*-ε4 and late-life cognition suggests that higher education is associated with cognitive reserve even among *APOE*-ε4 carriers.

This dissertation provides information on patterns of cognitive state changes and their predictors in older adults that will benefit older adults, their families, and the healthcare system. Patterns of cognitive trajectories among older adults are diverse, complex, and difficult to identify. Advanced statistical approaches and their software applications are developed for modeling complex longitudinal cognitive trajectories; however, integrating clinically-driven approaches in identifying distinct patterns of cognitive state changes is beneficial. The results of this dissertation show that higher academic achievement may increase the odds of cognitive reserve by leading to healthier

cognitive trajectories. While *APOE*-ε4 and older age are non-modifiable risk factors for dementia, it may be possible to compensate for their detrimental effects through a modifiable factor, such as graduate-level education. Therefore, investing in higher education is an important potential intervention that may prevent or delay dementia even among individuals carrying a genetic risk factor. Furthermore, it may be worthwhile for researchers targeting *APOE* to develop interventions that consider non-genetic factors that may modify the effect of *APOE* on cognition.

Acknowledgements

I would like to express my deepest gratitude to my co-supervisors Dr. Suzanne Tyas and Dr. Joel Dubin. Dr. Tyas, I greatly appreciate your excellent and constant supervision. Thank you for your inspiration, encouragement, patience, and smiles. Forever, I will be thankful for your endless support. Thank you, Dr. Dubin, for your great supervision, support, and for helping me to grow in my confidence to use complex statistical methods.

I want to give my sincere thanks to Dr. Colleen Maxwell and Dr. Philip St. John. Dr. Maxwell, you always went above and beyond in your role as a committee member. I will forever be thankful for your superb advice and kind support. Dr. St John, thank you for your great comments and questions. In addition, thank you for validating the clinical sense of my results.

I would like to acknowledge my examiners, Dr. Cecilia Cotton and Dr. Roger Dixon. Thank you both for your insightful comments and questions on my dissertation. I would like to acknowledge Dr. Mary Thompson and Dr. Mu Zhu for encouraging and supporting me to start this PhD while completing my Master's degree in Statistics.

I would like to thank all the present and the past members of the Epidemiology of Cognitive Aging and Resilience Research Group who were cheering me on during my progress. Each of you are/were valuable members of the group and I would like to thank you all for your support and for our good memories. Thank you, Dr. Tyas, for your support of my idea to start the writing in network group and thank you those who joined the group. I learned and grew significantly as a result of that.

A special thanks to Dr. Philip Bigelow, Dr. Shannon Freeman, Dr. Kelly Skinner, Tracy Taves, Janne Janke, Mary McPherson, Dr. Svitlana Taraban-Gordon, Dr. Stephanie White, Dr. Christine Zaza, Dr. Leila Jalali, Dr. Shahla Aliakbari, Dr. Masoomeh Rudafshani, Dr. Nasim Paryab, Dr. Saeedeh Akram, Dr. Nafiseh Nafisi, Dr. Mahtab Kamali, Dr. Shahin Toobaee, Maryyeh Chehrehsaz, Dr. Atefeh Zarabadi, Dr. Homeyra Pourmohammadali, Dr. Narges Simjour, Afsaneh Rezaee, Raheleh Mohammadi, and Bita Roshanaei. Your inspiration and support made my PhD program an extraordinary experience.

I would like to thank the participants of the Nun Study and the primary researchers who initiated and continued the study over several years. I also acknowledge the initial funding of the Nun Study at

the University of Minnesota and at the University of Kentucky: NIA 5R01AG09862, K04AG00553, P50AG05144, and the Kleberg Foundation. In addition, I would like to acknowledge the funding of this study at the University of Waterloo from the Canadian Institutes for Health Research (CIHR) MOP 137035, from the Natural Sciences and Engineering Research Council of Canada (NSERC) discovery grant, from the Royal Bank of Canada (RBC)/UW Applied Health Sciences Partnership Fund, Aging and Retirement Grants, and the Network on Aging Research (NAR) Catalyst Grant.

I am extremely grateful to my parents, Fatemeh Nayyer and Mohammad-Bagher Iraniparast. Thank you for your infinite love, support, and encouragement. I would like to warmly thank my siblings and other dear family members, Mitra, Soheila, Katy, Mehrzad, Alireza, Hasti, Mercedeh, Kiana, Kimia, Mahshid, Sohrab, Nasrin, Nayyereh, Naimeh, Mahmood Golchin, Kaveh Kamali, Hadi Iraniparast, Robab Bahari, and Seyed-Ali Zamanzadeh whose inspiration and support travels over the oceans and mountains to reach me.

Last but foremost, I would like to express my loving gratitude to my husband, Mirzaman. Thank you for believing in me and supporting me. Great thanks to our amazing and lovely son, Matin. You are the beauty of our life and the joy of our moments.

This dissertation is dedicated to

my mother and father

for their infinite love and support ….

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List of Abbreviations

ADL	Activities of daily living
APOE	Apolipoprotein E, gene
ApoE	Apolipoprotein E, protein
BIC	Bayesian information criteria
CDR-SB	Clinical Dementia Rating—Sum of Boxes
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence interval
GI	Global impairment
GPA	Grade point average
lcmm	Latent class mixed-effects modeling
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
OR	Odds ratio

Chapter 1
Introduction

1.1 Cognitive aging

Cognitive aging refers to changes in cognitive abilities over time. Similar to cognitive aging earlier in life, cognitive aging later in life (typically defined as age 65 years and older) is a continuum (Petersen, 1995; Petersen et al., 1997). Among older adults, normal cognitive aging is maintaining a level of cognitive ability that is typical for older adults who, with aging, might experience some levels of cognitive decline but have reasonably normal cognitive function (Petersen et al., 1997; Schaie, 1994). However, cognitive decline in older adults might exceed that typical age-related level of impairment and decline further to mild cognitive impairment (MCI) and dementia (Petersen et al., 1997). While standardized diagnostic criteria for MCI and dementia do not exist yet (Christa Maree Stephan et al., 2013), the clinical relevance of these states is recognized, as is the importance of studying the range of cognitive states from normal cognition to dementia to understand cognitive aging in older adults. In this thesis, the whole spectrum of cognitive aging is studied and referred to as changes in cognitive abilities over time among older adults.

1.1.1 Normal cognitive aging, cognitive decline, and dementia

Dementia is an umbrella term to describe a collection of clinical symptoms of cognitive impairment in multiple domains that interfere with activities of daily living (Tyas & Gutmanis, 2015; Voelker, 2008). Dementia has several causes with Alzheimer's disease being the most common, accounting for approximately two-thirds of cases (American Psychiatric Association, 1994; Chouliaras, Topiwala, Cristescu, & Ebmeier, 2015; Prince et al., 2013), and vascular dementia being the second most common, accounting for approximately 5 to 10% of cases (Alzheimer's Association, 2019). It has been increasingly recognized that Alzheimer and vascular pathology frequently overlap, with pure Alzheimer pathology much less common than

initially thought, particularly in the oldest age groups (Rahimi & Kovacs, 2014; Schneider, Arvanitakis, Bang, & Bennett, 2007).

Clinically, individuals who develop dementia start with normal cognitive aging and usually go through an MCI phase before developing dementia. This process is described by the *cognitive continuum* model (Petersen, 1995; Petersen et al., 1997). Types of dementia have diverse timings and etiology, with typical pathological changes underlying the most common subtypes. For example, Alzheimer pathology—amyloid plaques and neurofibrillary tangles—is thought to begin 20 to 30 years before deterioration reaches a level that leads to clinical symptoms of cognitive impairment or dementia (Fisher, Plassman, Heeringa, & Langa, 2008; Howieson et al., 2003; Jack et al., 2013; Nilsson et al., 2010; Perneczky et al., 2006; Rijal Upadhaya et al., 2014; Sperling et al., 2011). Similarly, the pathology associated with vascular dementia—cerebrovascular disease due to arteriosclerotic changes in the cerebral vasculature—begins a long time prior to reaching a level to cause clinical cognitive impairment or dementia, or causing the stroke which in turn may lead to post-stroke dementia (Kalaria, 2018).

1.1.2 Impact of dementia

Normal cognitive aging is associated with well-being and health-related quality of life (Davis et al., 2015). However, the majority of older adults experience some level of cognitive impairment (Petersen, 2011). Prevalence and level of cognitive impairment increase with aging. For example, dementia affects about 5% of older adults 65 years and older, and 30% of those 80 and over (Jorm, Korten, & Henderson, 1987; Ritchie & Lovestone, 2002). Therefore, older age is a major risk factor for cognitive decline and dementia (Jagger & Lindesay, 1993; Tyas & Gutmanis, 2015; World Health Organization, 2012). Worldwide, the population of older adults is increasing. The global population of older adults was 654 million (8.7% of the world's population) in 2017 (World Bank, 2017) and it is anticipated to increase to 1.6 billion by 2050 (16.7% of the world's population) (He, Goodkind, & Kowal, 2016). With these projected

increases in the number of older adults, the global prevalence of dementia is also expected to increase.

Dementia is the most feared aspect of the aging experience (Bazalgette et al., 2011). It is one of the most disabling health conditions and is a major public health problem (Ferri et al., 2005; Tyas & Gutmanis, 2015). With limited treatment success, research focusing on patterns of cognitive state changes and their predictors provides information for older adults and opens windows for preventing or delaying the onset of dementia (Singh-Manoux & Kivimäki, 2010; Voelker, 2008).

1.1.3 Assessment of cognition

Cognition can be assessed as an overall ability (e.g., based on performance on a global cognitive test, such as the Mini-Mental State Examination (MMSE)) or in relation to various domains—such as attention, executive function, learning and memory, language, motor function, and social cognition—using neuropsychological tests (American Psychiatric Association, 2013). To diagnose the cognitive state of an older adult, overall cognitive ability, performance in specific cognitive domains, and activities of daily living (ADL) are assessed and compared over time (M. S. Albert et al., 2011; McKhann, Drachman, & Folstein, 1984; McKhann et al., 2011; Riley, Snowdon, & Markesbery, 2002). The cognitive continuum is usually categorized into three cognitive states: intact cognition, a cognitive impairment state less severe than dementia (e.g., MCI), and dementia (Kryscio, Schmitt, Salazar, Mendiondo, & Markesbery, 2006; Petersen, 1995).

Results of cognitive assessments are most useful when compared longitudinally. For example, on tests such as the MMSE, older adults with cognitive impairment and high levels of educational attainment may earn scores typically associated with normal cognition. Conversely, among older adults with low levels of educational attainment, those with normal cognition may earn low MMSE scores. In clinical practice, scores on cognitive tests are most useful to quantify

cognitive trajectories over time (Small et al., 1997)—i.e., examining cognitive change over time in the same individual.

1.2 Longitudinal trajectories of cognitive aging

Studying longitudinal trajectories of cognitive aging is superior to investigating cognitive aging in cross-sectional studies because the latter provides a snapshot of just one point in the cognitive trajectory and cannot identify the cognitive state changes over time. Given that cognitive deterioration may start 20 years before the onset of dementia (Sperling et al., 2011), and that risk factors can influence cognitive trajectories during these decades before dementia (Tyas et al., 2007), understanding trajectories early in the process of cognitive decline as well as the predictors of healthier cognitive trajectories will support initiatives to build cognitive reserve and prevent or delay cognitive impairment or dementia.

Currently, cognitive trajectories have been studied with three perspectives: 1) transition between cognitive states; 2) trajectories of specific domains; and 3) trajectories of overall cognition, based on overall cognition tests (e.g., MMSE) or on a combined score calculated from tests on specific domains. Literature on longitudinal trajectories of cognitive aging is presented in Chapters 2 and 4. The overall patterns of cognitive trajectories based on cognitive states are not well characterized, even though cognitive states (e.g., normal cognition, MCI, and dementia) are the primary ways cognition is described in clinical practice.

1.3 Factors associated with longitudinal trajectories of cognitive aging

To increase the chance of healthy cognitive aging, it is important to identify its predictors. Other than aging, genetic and non-genetic factors may interact to increase the risk of cognitive impairment or its progression to dementia (Bagyinszky, Youn, An, & Kim, 2014). In this thesis, the effect of sociodemographic factors, intellectual factors, and apolipoprotein E (*APOE*), the most important genetic risk factor for dementia and more specifically for Alzheimer's disease (Bagyinszky et al., 2014), will be studied. In addition, two theories of aging will be tested: the antagonistic pleiotropy theory and the complementary scaffolding theory of aging and cognition.

The antagonistic pleiotropy theory for an allele is a concept in evolutionary biology that refers to beneficial effects of an allele earlier in life and its adverse effects later in life (Medawar, 1952; Williams, 1957). The scaffolding theory of aging and cognition may clarify how a combination of adverse and compensatory neural processes may influence cognition later in life (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). In this thesis, the antagonistic pleiotropy hypothesis will be tested by studying the effect of *APOE* on cognition earlier and later in life—through the association of *APOE* with educational attainment earlier in life and with patterns of cognitive state changes later in life. The scaffolding theory of aging and cognition will be tested by studying whether higher educational attainment may compensate for the detrimental effects of the ε4 allele of *APOE* gene on cognition. Literature on the effect of sociodemographic factors and intellectual factors on cognitive aging is presented in Chapters 3 and 5. Literature on the effect of *APOE* on cognition earlier and later in life is presented in Chapters 3 and 6.

1.4 Goals and implications

Learning about cognitive decline prior to dementia and prevention of dementia is a public health priority. This dissertation identified patterns of cognitive state changes and factors associated with experiencing these different patterns. Using clinically-driven and statistical modeling approaches, this research identified patterns of cognitive state changes through four cognitive states ranging from normal cognition to dementia, with two intermediary cognitive impairment states in between. Then, the association between academic achievement—educational attainment and academic performance—and experiencing different patterns of cognitive state changes was investigated. Finally, a life-span effect of a genetic factor on cognition was tested. This longitudinal analysis of patterns of cognitive state changes and their predictors is among the first studies that has evaluated cognitive aging as overall cognitive states and examined their potential predictors.

The results of this dissertation will contribute to the knowledge of expected patterns of age-related cognitive state changes and their predictors, providing valuable information for older adults, their families, care partners, and healthcare systems in planning for care, treatment, and support. Furthermore, researchers designing clinical trials for intervention will benefit from this knowledge for planning those trials, including the recruitment of participants. In addition, knowledge of patterns of cognitive state changes will provide an opportunity to investigate the effect of established risk factors for dementia on patterns of cognitive state changes.

Chapter 2
Literature Review

This chapter presents an overview of the literature on cognitive aging in older adults and the effect of academic achievement and apolipoprotein E (*APOE*) on cognitive aging. One of the most frequently asked questions regarding cognition later in life is about the potential patterns of cognitive state changes and their predictors. The temporal changes in cognitive states are not well characterized, even though cognitive states (e.g., normal cognition, mild cognitive impairment [MCI], and dementia) are the primary ways cognition is described in clinical practice. Preliminary research has attempted to identify the potential patterns of cognitive state changes among older adults. However, due to the limited availability and the complexity of the analytical approaches to analyze longitudinal ordinal cognitive states, in contrast to continuous cognitive outcomes, researchers have not examined the trajectories of cognitive state changes in much detail. However, research on other aspects of cognitive aging in older adults has identified heterogeneity in cognitive function upon reaching older age, in rates of cognitive decline, and in potential improvements to a higher cognitive level that suggest the importance of attention to such details when modeling trajectories of cognitive state changes.

2.1 Cognitive aging

Cognitive aging among older adults is usually assumed to follow a decline trajectory. However, both earlier (Brayne, Huppert, Paykel, & Gill, 1992; Lyketsos, Chen, & Anthony, 1999) and more recent studies (Malek-Ahmadi, 2016; Xue et al., 2019) provide growing evidence that cognitive aging is heterogeneous among older adults and includes stable MCI and improvement from MCI to normal cognition.

The foundation for research on trajectories of cognitive state changes in older adults has been established based on studying cognitive aging: 1) within specific domains such as learning or memory; 2) through tests that measure overall cognition using a single test such as the Mini-Mental State Examination (MMSE) or Clinical Dementia Rating—Sum of Boxes (CDR–SB); or

3) using a more comprehensive measure of cognition based on composite scores across multiple cognitive tests and domains. Some studies have considered more than one of these measures to model trajectories of cognitive aging (Bretsky et al., 2003; McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016; D. Mungas et al., 2010). For example, Zaninotto et al. (2018) studied three cognitive domains (memory, executive function, and processing speed) and a global cognitive function based on these three domains to study cognitive aging. They showed that postsecondary education was associated with higher levels of memory, executive function, processing speed, and global cognitive score, and with a faster decline in global cognitive function. A limitation of the study by Zaninotto et al. (2018), however, is that in their analytic sample of 10,626 individuals, the heterogeneity of cognitive decline was not fully considered because only one overall cognitive aging trajectory was modelled, and individual variability may be more than the differences between individuals reflected in an overall baseline score or rate of decline.

Other studies have chosen to capture the heterogeneity of cognitive decline with several patterns (Baker et al., 2017; Hofer et al., 2002; McCarrey et al., 2016; D. Mungas, Early, Glymour, Zeki Al Hazzouri, & Haan, 2018; Thibeau, McFall, Camicioli, & Dixon, 2017; Yaffe et al., 2009). For example, Barker et al. (2017) identified six distinct patterns in MMSE scores to describe cognitive aging in their analytic sample of 3441 individuals. Individuals in these six patterns had five different levels of MMSE at baseline, and two patterns with similar cognitive levels at baseline had different rates of decline. A limitation of this study is in their measure of cognition, which was based on only one type of test, and in not capturing any potential stable cognition or reversion to a higher MMSE score for some individuals.

Fewer studies have examined composite scores across multiple cognitive tests or domains to identify points of change in rate of cognitive decline (Wilson et al., 2012). Wilson et al. (2012) showed an association between more years of education and a delay in increased accelerated decline (when clinical diagnosis of dementia occurs at an older age for individuals with higher than with lower educational attainment, but once reserve is exhausted and decline begins, this

decline is faster in those with higher educational attainment). One aspect of cognitive aging that was missed in this study was consideration of trajectories with cognitive improvement versus cognitive decline. The authors presented a figure for individual cognitive trajectories, which displayed patterns of both improvement and decline among participants (Wilson et al., 2012). This aspect of cognitive trajectories most often has been studied in modeling transitions between cognitive states as ordinal cognitive outcomes based on combining scores across multiple cognitive tests (Abner et al., 2012; Wei & Kryscio, 2016). For example, Wei et al. (2016) found that carrying a genetic risk factor for dementia (apolipoprotein E-ε4 (*APOE*-ε4)) and low levels of education (high school or less) was associated with lower odds of reversion from MCI to normal cognition. A limitation of such studies that model both reverse transitions from MCI to normal cognition and progression to MCI and dementia, however, is that they miss modelling the temporal changes in cognitive states.

A study by Aiken-Morgan et al. (2017) found four distinct patterns of cognitive state changes with temporal changes in cognitive states that included both reversion from MCI to normal cognition and progression from MCI to dementia. However, they did not provide information on the analytic method used to identify the patterns of cognitive state changes. Description of the methods used to identify distinct patterns of cognitive state changes is important because analyzing longitudinal data on aging and cognition is complex; to contribute to progress in research on modeling patterns of cognitive state changes, clear analytical methodology is required that can be replicated and improved.

Studies of aging in cognitive domains provide useful information on cognitive aging within domains and also model trajectories with improvement to better cognitive function. However, these studies do not provide a global perspective that identifies whether individuals who experienced improvement within one domain also experienced improvement within other domains, or whether their overall cognitive state declined or improved when experiencing trajectories of decline and improvement within domains. Also, studies of transitions between cognitive states do not provide a comprehensive picture of temporal changes in cognitive states.

2.2 Education and cognitive reserve

Lower education is associated with higher prevalence of dementia (Zhang et al., 1990), and higher education is considered to contribute to cognitive reserve (Y. Stern, Albert, Tang, & Tsai, 1999). It is suggested that cognitive reserve is the ability of a brain with damage to function at a normal level or at least a higher level than would be expected with that level of brain damage (Y. Stern, 2002; Y. Stern, 2009; Y. Stern et al., 1999). In addition, lifetime cognitive stimulation is suggested to delay or even prevent brain damage through delaying hippocampal atrophy (Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008) or preventing accumulation of amyloid plaques (Landau et al., 2012).

Longitudinal studies of aging and cognition have observed that educational attainment is associated with potential cognitive reserve as shown through four categories of evidence on the effects of higher educational attainment: 1) higher cognitive performance upon reaching older adulthood (Alley, Suthers, & Crimmins, 2007; McDermott, McFall, Andrews, Anstey, & Dixon, 2016; D. Mungas et al., 2018; Muniz-Terrera et al., 2009; Tucker-Drob, Johnson, & Jones, 2009; Wilson et al., 2019; Zahodne et al., 2011; Zahodne, Stern, & Manly, 2015); 2) slower cognitive decline compared to older adults with lower educational attainment (Alley et al., 2007; McDermott et al., 2016; Reas et al., 2017; Zahodne et al., 2015); 3) delayed accelerated decline (when clinical diagnosis of dementia occurs at an older age for individuals with higher than with lower educational attainment, but once reserve is exhausted and decline begins, this decline is faster in those with higher educational attainment (Castro-Costa et al., 2011; Clouston et al., 2019; Hall et al., 2007; Wattmo, Londos, & Minthon, 2014); and 4) greater probability of reversion from MCI to normal cognition (Canevelli et al., 2016; Iraniparast et al., 2016).

The first two of these four categories on how higher educational attainment increases the chance of cognitive reserve are usually studied together. For example, Alley et al. (2007), McDermott et al. 2016, and Zahodne et al. (2015) have found an association between higher education and higher cognitive performance upon reaching older adulthood and also slower cognitive decline compared to older adults with lower educational attainment. On the other hand,

some studies examining these two categories have only found a significant association between higher education and higher cognitive performance upon reaching older adulthood, and not slower cognitive decline compared to older adults with lower educational attainment (D. Mungas et al., 2018; Tucker-Drob et al., 2009; Wilson et al., 2019; Zahodne et al., 2011). Several methodological aspects of these studies could have led to such a discrepancy in the results (e.g., differences in age of the analytic sample at baseline, length of follow-up in the longitudinal study, measures of cognition, levels of education and other characteristics of the sample, sample size, and analytical approach). For example, in the study by Zahodne et al. (2011), using linear growth modeling, higher education was only associated with cognition at baseline and not with rate of cognitive decline. However, in another study by Zahodne et al. (2015), using second-order latent growth curve modeling, higher education was associated with both cognition at baseline and slower cognitive decline. While these two studies had many other different characteristics, the differences in analytic approach could explain the variation in results since in another study by McDermott et al. (2016) using latent growth mixture modeling, higher education was again associated with higher cognitive level at baseline and slower rate of decline. Using nonlinear latent growth curve modeling, McArdle (2011) showed that individuals with higher education had higher cognitive scores at all ages.

An example of a study that investigated cognitive reserve through the association between education and cognitive decline is by Hall et al. (2007). In a sample of incident cases of dementia, they found that more years of education were associated with a delay in the rate of accelerated cognitive decline, with increasing years of education associated with more delay and faster decline. Finally, studies on the association between education and transitions between cognitive states found that higher education was associated with an increased odds of reversion from MCI to normal cognition (Canevelli et al., 2016; Sachdev et al., 2013; Xue et al., 2019).

The first three categories of evidence on how educational attainment is associated with cognitive reserve among older adults modeled cognition through temporal cognitive trajectories. Although reverse transitions were observed in single cognitive trajectories, for example

trajectories of change in memory scores (Hall et al., 2007), these studies did not identify whether individuals with higher education experienced cognitive improvement (i.e., reversion to a less impaired state). Therefore, individual cognitive trajectories with improvements were combined with individual trajectories of cognitive impairment contributing to an average cognitive decline. On the other hand, although reversion is investigated in the fourth category of evidence, these studies did not model temporal cognitive trajectories for individuals who experience reverse transitions, such as whether those who experience reverse transitions eventually developed dementia.

2.3 Apolipoprotein E and cognition

2.3.1 Apolipoprotein E and cognition earlier in life

The association between *APOE* and cognition has been studied in children and younger adults. Previous research on the effect of *APOE* on cognition has shown that the *APOE*-ε4 allele may be associated with higher cognitive abilities earlier in life. In children and young adults, *APOE*-ε4 was associated with better cognitive performance as reflected in infant development (Wright et al., 2003), visuospatial processing (Bloss, Delis, Salmon, & Bondi, 2010), verbal fluency (Marchant, King, Tabet, & Rusted, 2010), decision making (Marchant et al., 2010), neuropsychological tests (Han & Bondi, 2008), IQ scores (Yu, Lin, Chen, Hong, & Tsai, 2000), and educational attainment (Hubacek et al., 2001). However, other studies have not found this beneficial effect of *APOE*-ε4 on cognition earlier in life (Bretsky et al., 2003; O'Donoghue, Murphy, Zamboni, Nobre, & Mackay, 2018).

2.3.2 Apolipoprotein E and cognition later in life

For the first time in 1993, the ε4 allele of the *APOE* gene was observed to be associated with Alzheimer's disease, the most common type of dementia (Corder et al., 1993; Strittmatter et al., 1993). Since then, the effect of *APOE*-ε4 on Alzheimer's disease has been replicated in hundreds of epidemiological studies, and *APOE*-ε4 has become the most widely accepted genetic risk

factor for Alzheimer's disease (Ali, Smart, & Gawryluk, 2018; Y. Liu et al., 2015; Ward et al., 2012). Other than the effect of *APOE*-ε4 on Alzheimer's disease, *APOE*-ε4 increases the risk of all-cause dementia (Llewellyn et al., 2010) and cognitive impairment less severe than dementia (Oveisgharan et al., 2018; Sun et al., 2018; Tyas et al., 2007).

2.3.2.1 The biological effect of apolipoprotein E-ε4 on increasing the risk of dementia

The *APOE* gene exerts its effect in the body through the apoE protein (Roses, 1996). ApoE is the most prevalent brain lipoprotein, is the main carrier of cholesterol in the brain, and is involved in neuronal maintenance and repair (Bagyinszky et al., 2014; Michaelson, 2014). Among human organs, the brain has the highest level of cholesterol (Shobab, Hsiung, & Feldman, 2005). An important role of apoE is to clear cholesterol from the brain extracellular matrix (Heverin et al., 2004). Individuals coding the ε4 type of the apoE protein cannot properly transport cholesterol from the brain to the bloodstream (Shobab et al., 2005). This impairment in clearing cholesterol from the brain is associated with the formation of extracellular amyloid plaques (Shobab et al., 2005).

In general, apoE is observed in both amyloid plaques and neurofibrillary tangles, neuropathological brain damage associated with Alzheimer's disease (Namba, Tomonaga, Kawasaki, Otomo, & Ikeda, 1991). However, based on autopsy assessment of those with Alzheimer's disease, being *APOE*-ε4-positive was related to more frequent plaques and tangles than being *APOE*-ε4-negative (Hansen et al., 1994; Nagy et al., 1995; Schmechel et al., 1993). In addition, those with Alzheimer's disease who were *APOE*-ε4-positive showed more severe brain degeneration than those who were *APOE*-ε4-negative and also showed significantly more impaired synaptic plasticity (Arendt et al., 1997), hippocampal atrophy (Poirier et al., 1995), and brain inflammation (Egensperger, Kosel, von Eitzen, & Graeber, 1998). Therefore, a wide range of evidence shows that *APOE*-ε4 is related to the main pathological hallmarks of Alzheimer's disease (Belinson & Michaelson, 2009).

2.3.2.2 Therapeutic approaches based on apolipoprotein E-ε4

Despite numerous research efforts, a cure for dementia has yet to be discovered and no treatments affect the course of the disease (Fereshtehnejad, Johnell, & Eriksdotter, 2014; Gauthier et al., 2012; Kryscio et al., 2013; Mangialasche, Kivipelto, Solomon, & Fratiglioni, 2012; Richens et al., 2013; Ungar, Altmann, & Greicius, 2014). Current strategies for controlling dementia are based on treatments that help to manage the symptoms for mild to moderate dementia (Ho et al., 2019; Iqbal, Gong, & Liu, 2014; Richens et al., 2013; Trivedi et al., 2019). After a number of phase III clinical trials that targeted amyloid plaques for developing a cure for Alzheimer's disease failed, *APOE*-ε4 is being considered as a new therapeutic target (Bales & Paul, 2019; Safieh, Korczyn, & Michaelson, 2019; Uddin et al., 2019). To develop a therapeutic strategy for prevention, researchers need to know how *APOE*-ε4 is associated with the trajectory of cognitive decline.

2.3.3 Apolipoprotein E and cognition earlier and later in life (antagonistic pleiotropy)

Combining the studies of the association between *APOE* and cognition both earlier and later in life shows that while *APOE*-ε4 is a risk factor for dementia, *APOE*-ε4 carriers may benefit from carrying this allele earlier in life. The *APOE* gene has thus been suggested to have an antagonistic pleiotropy effect on cognition (Alexander et al., 2007; Tuminello & Han, 2011; Wright et al., 2003). The theory of antagonistic pleiotropy was first introduced in the field of evolutionary biology by Medawar (1952) and Williams (1957). A potential antagonistic pleiotropy effect for a gene refers to a potential beneficial effect of a genetic allele earlier in life contrasted with its adverse effects later in life.

Tuminello & Han (2011) suggested that because the effect of *APOE*-ε4 on cognition differs among younger and older individuals, assessing the interaction between age and *APOE*-ε4 when studying the effect of *APOE*-ε4 on cognition may be a valuable addition to investigations of the antagonistic pleiotropy hypothesis. However, previous research on *APOE*-ε4 and cognition earlier and later in life has been performed on separate samples (Corder et al., 1993; Spinney,

2014; Wright et al., 2003); therefore, this interaction cannot be tested in these studies. One study by Luciano et al. (2009) that investigated the effect of *APOE*-ε4 on cognition was a stratified analysis for the effect of *APOE* on cognition both earlier and later in life within the same cohort of individuals. This research did not show a significant association between *APOE*-ε4 and IQ in early life; however, it did show a significant association between *APOE*-ε4 and lower nonverbal cognition in old age.

2.3.4 The scaffolding theory of aging and cognition as a complementary theory to the antagonistic pleiotropy hypothesis

The scaffolding theory of aging and cognition (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014) is a theoretical model more recent than, and complementary to, the antagonistic pleiotropy hypothesis. This scaffolding theory aims to clarify how a combination of adverse and compensatory neural processes may influence cognitive aging. A compensatory neural process suggests recruitment of additional neuronal paths in the brain avoids the detrimental effects of adverse factors on cognitive aging. This is complementary to the antagonistic pleiotropy effect of *APOE*-ε4 on cognition, suggesting that *APOE*-ε4 carriers with higher educational attainment (even if their higher educational attainment is not due to an earlier beneficial effect of the *APOE*-ε4 allele) may have a combination of at least two factors: one that has an adverse effect on cognition (carrying an *APOE*-ε4 allele) and one that has a compensatory effect on cognition (higher educational attainment). These factors may interact to influence cognitive aging. Therefore, according to the scaffolding theory of aging and cognition it may be assumed that *APOE*-ε4 carriers with high educational attainment, which might be due to the beneficial effects of *APOE* on early-life cognition, may develop a reserve that will compensate for the detrimental effects of *APOE*-ε4 on late-life cognition, such that their risk of dementia would be similar to *APOE*-ε4 non-carriers. Thus far, several studies have found that higher educational attainment earlier in life could modify the detrimental effect of *APOE*-ε4 on cognition later in life (Arenaza-Urquijo et al., 2015; Reas et al., 2019; Tyas et al., 2007) although other studies have not found higher education to reduce the risk of dementia or Alzheimer's disease among *APOE*-ε4 carriers

(Ngandu et al., 2007). It has also been suggested that such an interaction may only be present among men (Hasselgren et al., 2019).

Overall, while some evidence indicates that higher education may modify the effect of *APOE*-ε4 on cognition among older adults, these studies have not determined whether *APOE*-ε4 is also associated with higher educational attainment earlier in life. Therefore, evidence is lacking on the interaction between age (i.e., early life and late life) and *APOE*, and its impact on cognition.

Chapter 3
Study Rationale and Research Questions

3.1 Study rationale

Cognitive transitions that lead to developing MCI and dementia follow unique linear and nonlinear patterns in cognitive domains over years (Howieson et al., 2008; Sperling et al., 2011). This long period is associated with complex cognitive trajectories, such as remaining in the normal cognitive state, reversion from MCI to normal cognition, or gradually declining towards dementia. Identifying the patterns of cognitive trajectories with aging and their predictors will provide crucial information for older adults, their families, and the healthcare system in planning for care, treatment, and support.

Few studies have investigated the full spectrum of trajectories of overall cognition and their predictors (Aiken-Morgan, Gamaldo, Wright, Allaire, & Whitfield, 2017; M. Albert, Blacker, Moss, Tanzi, & McArdle, 2007; Karlamangla et al., 2009; Wilson et al., 2012). In addition to studies of the transitions between cognitive states, cognitive trajectories have been studied focusing on three types of cognitive measures: 1) specific cognitive domains; 2) specific cognitive tests (e.g., MMSE); and 3) composite scores across multiple cognitive tests and domains. However, the overall patterns of cognitive trajectories based on cognitive states are not well characterized, even though cognitive states (e.g., normal cognition, MCI, and dementia) are the primary ways cognition is described.

While the adverse effect of *APOE*-ε4 on late-life cognitive trajectories has been investigated using longitudinal studies (Albrecht et al., 2015; Hofer et al., 2002; Iraniparast et al., 2016; Tyas et al., 2007), its effect on the trajectories of overall cognitive state changes is not established. In addition, the potential beneficial effect of *APOE*-ε4 on educational attainment in the same population who will be studied for their later-life cognitive trajectories has not been studied before, and how educational attainment might modify the effect of *APOE*-ε4 on those trajectories remains unclear. In this dissertation, the patterns of overall cognitive state changes were

identified and the association between specific risk factors and these cognitive trajectories were examined.

For the first question of this dissertation, patterns of cognitive trajectories were identified using two distinct approaches: 1) a clinically-driven method and 2) a statistical modeling approach, *latent class mixed-effects modeling* (*lcmm*). This statistical method for analyzing longitudinal data considers both the mixed modeling theory that accounts for correlation between repeated longitudinal measurements for individuals, and the latent class modeling theory that discriminates homogeneous latent classes (Proust-Lima, Philipps, & Liquet, 2017) (see Section 4.2.3.2). Then, the latent classes identified using the statistical modeling approach were compared with classes identified using the clinically-driven approach.

The potential predictors of these patterns of cognitive trajectories were identified in Research Questions 2 and 3. For the second research question, the association between academic achievement (educational attainment and academic performance in high school) and patterns of cognitive trajectories were investigated. The effect of higher educational attainment on reduced risk of dementia is well established. In this dissertation, the effect on membership in patterns of cognitive trajectories of higher academic achievement that includes both educational attainment and better performance in high school courses was examined.

For the third research question, the effect of *APOE* on later-life patterns of cognitive trajectories was studied. *APOE*-ε4 is a risk factor for Alzheimer's disease, the most common cause of dementia. However, the effect of *APOE* on cognitive trajectories is not clear and may be modified by the level of education attained earlier in life (Shadlen et al., 2005). Based on the antagonistic pleiotropy hypothesis (Williams, 1957), although carrying an *APOE*-ε4 allele is a risk factor for cognitive decline later in life, it may have beneficial effects in early life, increasing the probability of attaining a higher level of education, which is a protective factor for dementia (Tuminello & Han, 2011).

3.2 Research questions and hypotheses

The overall objective of this research is to identify the heterogeneous patterns of cognitive state changes, and to identify the factors associated with membership in these distinct patterns of cognitive trajectories.

Research Question 1: What are the patterns of cognitive state changes among older adults identified using a clinically-driven approach and a statistical modeling method, and how do the patterns of cognitive state changes identified using these two methods compare? (Chapter 4)

Hypothesis 1: Three categories of cognitive trajectories are expected to be observed: 1) fixed-state trajectories of cognitive impairment: individuals who remain in the same state of cognitive impairment (i.e., MCI, global impairment (GI), or dementia) over the study period; 2) trajectories that represent cognitive reserve (e.g., reflecting stable normal cognition or cognitive improvement): for example, individuals who show some level of cognitive impairment (MCI or GI) and then revert back to normal cognition; and 3) trajectories that represent gradual cognitive decline: for example, individuals who start with normal cognition, and then decline to MCI, GI, and possibly dementia.

Research Question 2: Is academic achievement—educational attainment and academic performance in high school—associated with cognitive reserve through membership in healthier patterns of cognitive state changes later in life? (Chapter 5)

Hypothesis 2: Higher levels of academic achievement are expected to be associated with cognitive reserve, reflected in a greater chance of experiencing healthier patterns of cognitive state changes, such as patterns with constant normal cognition, patterns with reverse transition from cognitive impairment to normal cognition, or patterns with cognitive decline without dementia.

Research Question 3: Is *APOE* associated with higher educational attainment earlier in life and with membership in the least healthy pattern of cognition later in life (i.e., does *APOE* have an

antagonistic pleiotropy effect on cognition)? Does higher education among *APOE*-ε4 carriers compensate for the detrimental effects of *APOE*-ε4 on cognition later in life? (Chapter 6)

Hypothesis 3: *APOE* has an antagonistic pleiotropy effect on cognition: carrying an *APOE*-ε4 allele is associated with higher educational attainment earlier in life, and higher risk of membership in the least healthy pattern of cognition later in life. *APOE*-ε4 carriers with higher educational attainment experience patterns of cognitive trajectories that are similar to non-carriers of *APOE*-ε4.

Chapter 4

Longitudinal Patterns of Cognitive State Changes among Older Adults: Comparing Results from Clinically-Driven and Statistical Modeling Methods

4.1 Introduction

One of the most frequently asked questions regarding cognition later in life is about the potential patterns of cognitive state changes, with particular concerns about the trajectory of cognitive decline to dementia. However, due to the limited availability and considerable complexity of the analytical approaches needed to analyze longitudinal ordinal cognitive states, researchers have not yet investigated the trajectories of cognitive state changes in much detail.

Cognition in late life is usually assumed to show a downward trajectory. However, longitudinal studies of aging and overall cognition show that, with aging, older adults experience improvement as well as decline in their cognitive performance. Research shows evidence of healthy cognitive aging (Brayne et al., 1992; Lyketsos et al., 1999) and improvement from mild impairment to normal cognition without eventual progression to dementia (Abner et al., 2012; Iraniparast et al., 2016; Koepsell & Monsell, 2012; Sachdev et al., 2013). Reports of these healthier patterns of cognitive aging are encouraging for older adults and their families, and are important for life and care planning for these individuals as well as the healthcare system.

The foundation for research on trajectories of cognitive state changes in older adults has been established based on studying cognitive performance as a continuous measure rather than as cognitive states. These foundational studies have assessed: 1) specific cognitive domains (Bretsky et al., 2003; Hall, Lipton, Sliwinski, & Stewart, 2000; Hofer et al., 2002; McCarrey et al., 2016; McDermott et al., 2016; D. Mungas et al., 2010; Singer, Verhaeghen, Ghisletta, Lindenberger, & Baltes, 2003; Thibeau et al., 2017; Zaninotto, Batty, Allerhand, & Deary, 2018); 2) specific cognitive tests (e.g., Mini-Mental State Examination (MMSE) or Clinical Dementia Rating—Sum of Boxes (CDR–SB)) (M. Albert et al., 2007; Baker et al., 2017; Brayne et al., 1992; Castro-Costa et al., 2011; Lyketsos et al., 1999; Yaffe et al., 2009); and 3) composite

scores across multiple cognitive tests (Karlamangla et al., 2009; Wilson et al., 2012). These longitudinal studies of aging and cognition show that older adults start their journey of cognitive aging at different levels and experience decline at diverse rates. These studies provide good information on cognitive aging within domains and individual and combined cognitive test scores, and also model trajectories with improvement. However, these studies do not provide information on the clinically important measure of overall cognitive function, and thus cannot identify whether individuals who experienced improvement within one domain (or individual or composite test score) also experienced improvement within other domains or tests, or whether their overall cognitive state declined or improved when experiencing trajectories of decline and improvement within domains.

To address this limitation, researchers have also focused on modeling overall cognitive states. Using neuropsychological tests of cognitive domains, tests of overall cognition, and abilities in activities of daily living (ADL), individuals are diagnosed with distinct cognitive states. Then, these cognitive states are modeled through transitions between cognitive states or through patterns of change.

Examples of studies that modeled *transitions between cognitive states* include modeling transitions from normal cognition to mild cognitive impairment (MCI) and from MCI to dementia (Kryscio, Yu, Snowdon, & Tyas, 2008; Riley et al., 2000; Tyas et al., 2007), or from MCI back to normal cognition (Abner et al., 2012; Iraniparast et al., 2016). Modeling transitions between cognitive states provides information on separate transitions between states; however, it does not provide information on temporal changes in cognitive states. Modeling patterns of cognitive state changes is an approach to address this limitation of modeling transitions between cognitive states. Studying *patterns of cognitive state changes* distinguishes temporal changes in cognitive state changes and can also identify distinct patterns. This perspective of studying patterns of cognitive state changes is similar to studies of specific cognitive domains when they identify distinct temporal patterns of change within cognitive domains.

The only study of patterns of cognitive state changes published to date is limited by its focus on sociodemographic characteristics of participants rather than on describing the methods used to identify the clusters of cognitive trajectories (Aiken-Morgan et al., 2017). Description of the methods used to identify distinct patterns of cognitive state changes is important because analyzing longitudinal data on aging and cognition is complex; to contribute to progress in research on modeling patterns of cognitive state changes, clear analytical methodology is required that can be replicated and improved.

Applying a clinically-driven approach allows allocation of individuals into different patterns of cognitive state changes that are clinically valid; however, it is a manual, time-consuming process and only a limited number of characteristics can be considered when assigning individuals into patterns. Automated analytic methods hold promise to address these limitations, but such methods have not yet been fully investigated. Previous research has applied latent class mixed-effects modeling (lcmm) (Proust-Lima et al., 2017) approaches to studies of preclinical dementia to identify temporal changes in cognition and daily functioning (Rajan et al., 2019; Verlinden et al., 2016) and to studies of Alzheimer's disease to identify distinct patterns of change in severity of clinical symptoms (Geifman, Kennedy, Schneider, Buchan, & Brinton, 2018). However, the validity of applying lcmm to identify latent classes of cognitive state changes in older adults in comparison to clinically-driven patterns of cognitive state changes has not been examined. The aims of this study were to identify and compare patterns of cognitive state changes among older adults using: 1) a clinically-driven approach, and 2) a statistical modeling method, lcmm.

4.2 Methods

4.2.1 Sample

This research is based on secondary data from the Nun Study, a longitudinal cohort study of aging and cognition. The participants are American members of a religious congregation, the School Sisters of Notre Dame. Between 1991 and 1993, all members who were 75 years or older and living in religious communities in the midwestern, eastern, and southern United States were

invited to join the Nun Study (N=1,031), and 678 (66%) volunteered to participate (Butler, Wesson, & Snowdon, 1996). These volunteers did not differ significantly from nonparticipants in their average age at baseline, mortality rate, race, and country of birth (Snowdon et al., 1996). The timeline of data collection for the Nun Study is presented in Figure 4-1. The analytic sample for this study is the 574 participants who had at least one follow-up cognitive assessment and could contribute to cognitive trajectories.

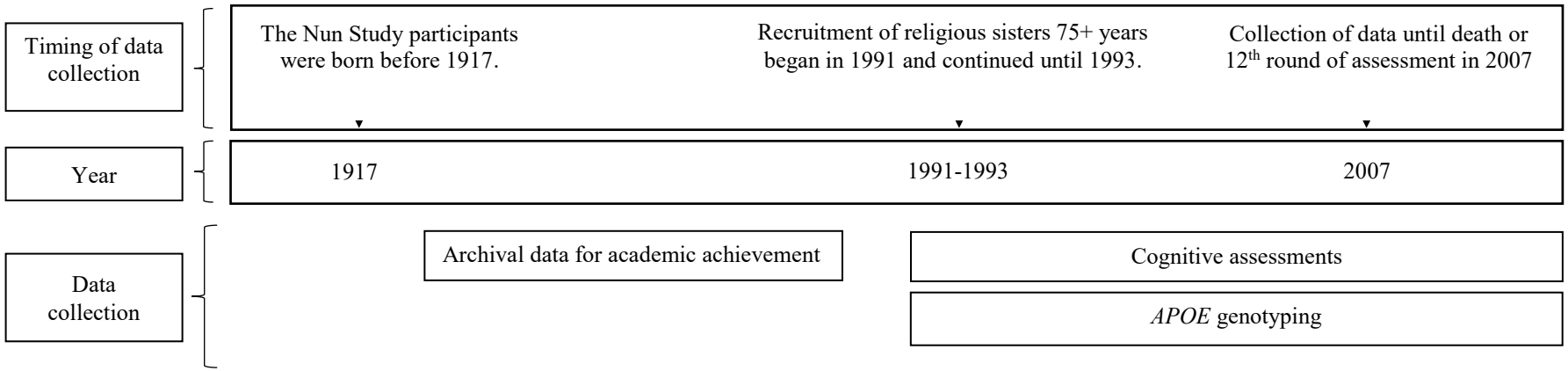

Figure 4-1 Timeline of data collection for the Nun Study

The longitudinal data on cognitive states for each participant were used to identify the patterns of cognitive state changes. These longitudinal data were based on approximately annual cognitive assessments from 1991 until death or the end of the 12th round of assessments. Individuals needed to have at least one follow-up cognitive assessment after their baseline assessment to be included in the longitudinal data analysis. In the Nun Study, 104 individuals had only one cognitive assessment (92 of these 104 died within two years of their initial assessment, reflecting the relatively low loss to follow-up in this sample other than through attrition by death). Therefore, for this study, the analytic sample is 678 – 104 = 574. More than 87% (504 out of 574) of the participants were followed until death. The remaining 70 individuals were alive at the end of the assessment period and thus their remaining cognitive trajectories until death were not observed.

4.2.2 Measures

Age at each cognitive assessment was calculated based on date of birth (from convent archives) and date of assessment. Cognitive state at each assessment was categorized as one of four mutually exclusive states: normal cognition, MCI, global impairment (GI), or dementia. The criteria for assigning individuals to these cognitive states have been described previously (Riley et al., 2002; Snowdon et al., 1996; Tyas et al., 2007) and are summarized briefly below and also in Appendix A, Table A-1.

Normal cognition. Participants with normal cognition had intact cognition in four cognitive tests (Riley et al., 2002) in the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (≥14 for Boston Naming, ≥12 for Verbal Fluency, ≥5 for Delayed Word Recall, and ≥9 for Constructional Praxis) (Morris et al., 1989; Welsh et al., 1994), intact global cognition based on the MMSE (≥24) (Folstein, Folstein, & McHugh, 1975), and intact function in at least four out of five performance-based ADL (i.e.,

feeding, dressing, walking, standing [transferring], and toileting) (Kuriansky & Gurland, 1976; Potvin et al., 1972).

Mild cognitive impairment. Participants with MCI were diagnosed based on having at least one specific area of impaired cognition (e.g., memory or naming) based on four cognitive tests from the CERAD neuropsychological battery, but with intact global cognition based on the MMSE (≥24), intact function in at least four out of five performance-based ADL, and not meeting criteria for dementia (Kuriansky & Gurland, 1976; Potvin et al., 1972). The cut-off point used for impairment in each test was 1.5 standard deviations below age-appropriate means, consistent with established definitions (Petersen et al., 1997; Petersen et al., 1999; Petersen, 2011; Smith, Petersen, Parisi, & Ivnik, 1996).

Global impairment. Participants with GI had impairment in global cognitive function (MMSE < 24), in performance-based ADL, or both. They were also impaired in at least one out of four tests from the CERAD neuropsychological battery. However, participants with GI did not meet criteria for dementia because if they had impairment in two areas of cognition, they were intact for performance-based ADL (≥4) (Riley et al., 2002; Riley, Snowdon, Desrosiers, & Markesbery, 2005).

Dementia. For a diagnosis of dementia, a participant had to have an impairment in memory and in at least one other cognitive domain based on the CERAD neuropsychological battery, impairment in performance-based ADL, and a decline from previous cognitive level (Snowdon et al., 1997). The cut-off point used for impairment in each test was identified

using scores below the 5th percentile of age norms in the CERAD battery (Morris et al., 1989; Welsh et al., 1994).

4.2.3 Analysis

The characteristics of the sample were described using standard univariate analyses. Then the patterns of cognitive state changes were identified based on two approaches: 1) a clinically-driven approach and 2) a statistical modeling method.

A participant's cognitive status at each assessment was recorded as an ordinal value with normal cognition representing the highest level of cognition followed by MCI and then GI; dementia represented the lowest level of cognition. The cognitive status assessments over time produce a sequence of longitudinal ordinal outcomes for each participant that we call a *single trajectory of cognitive state changes*. To identify the overall patterns of cognitive state changes for all participants, homogeneous trajectories were grouped together. Then, groups of individuals with distinct patterns of cognitive state changes were assigned to separate classes. The approaches to identify these distinct classes differ between the clinically-driven approach and the statistical modeling method.

Clinically-driven approach to identify distinct patterns of cognitive state changes

In the clinically-driven classification approach, single trajectories of cognitive state changes for all 574 participants were reviewed multiple times to identify different possible trajectories. Then, similar and dissimilar cognitive trajectories were defined based on the cognitive states that individuals experienced. Similarity of cognitive trajectories were defined based on whether individuals experienced stable or non-stable trajectories and, among non-stable trajectories, whether they experienced a reverse transition, developed dementia or both. Three categories of cognitive trajectories were expected to be observed: 1) fixed-state trajectories: individuals who remained in the same cognitive state (i.e., normal cognition, MCI, GI, or dementia) over the study period; 2) trajectories that represented cognitive

reserve (i.e., reflecting stable normal cognition or cognitive improvement): for example, individuals who experienced some level of cognitive impairment (MCI or GI) and then reverted back to normal cognition; and 3) trajectories that represented progressive cognitive decline: for example, individuals who started with normal cognition, and then declined to MCI, GI, and possibly dementia.

At this stage, the definition for the first pattern was created and the first individual was assigned to it. Then, the cognitive trajectory of the second individual was reviewed. If the cognitive trajectory of the second individual was similar to the first individual, with respect to stable and non-stable trajectories and reverse transition or dementia status, the second individual was assigned to the first pattern. However, if the cognitive trajectory of the second individual differed from that of the first individual, the second pattern was defined and the second individual was assigned to it. This process continued until all individuals were assigned to one pattern (see Appendix B, Table B-1 and Table B-2 for examples of similar cognitive trajectories across participants). The final patterns were reviewed by a geriatrician for clinical validation.

Statistical modeling approach to identify distinct classes of cognitive state changes

In the statistical modeling approach, lcmm (Proust-Lima et al., 2017) was implemented. In studies of longitudinal measurements of an outcome, lcmm considers both the mixed modeling theory that accounts for correlation between repeated longitudinal measurements for individuals, and the latent class modeling theory that discriminates homogeneous latent classes (Proust-Lima et al., 2017). The lcmm approach is particularly useful in identifying latent classes in longitudinal studies of aging because it is flexible in modeling unequal numbers of observations and different times of assessments (Proust-Lima et al., 2017).

In the Nun Study, the number of longitudinal observations for each participant ranged between 2 and 12 assessments, and these were performed at different dates during each wave

of follow-up assessments. The time scale that accounts for the repeated measurements for each individual in the mixed model was age, which also controls for the effect of age on patterns of cognitive state changes. Both linear and quadratic terms for age were added to the model to allow for the quadratic changes of cognitive states with aging (Amieva et al., 2005; Hall, Lipton, Sliwinski, & Stewart, 2000).

A random intercept term was added to the models to account for between-person heterogeneity of average cognition levels at baseline. In addition, a random slope term was added to the model to account for the potential variability of slope in each latent class over the follow-up period.

The modeling started with fitting one latent class and then the number of latent classes was increased until the model fit did not improve further. Model fit was evaluated by considering Bayesian information criteria (BIC), posterior class-membership probabilities, and clinical meaningfulness of classes (Proust-Lima et al., 2017). The model with the smallest BIC, posterior probabilities above 0.70, and meaningful classes was chosen as the preferred model, and the number of classes in that model as the number of latent classes for identifying distinct patterns of cognitive state changes. The posterior probabilities were computed using Bayes theorem when the probability of belonging to each latent class is calculated given the available information. The mean of the posterior probabilities is the average of posterior probabilities for all individuals classified *a posteriori* in each latent class. Models with and without a random intercept and random slope, and with and without a quadratic term for age were also fitted; however, the models with a random intercept and linear and quadratic terms for the effect of age provided a better fit.

For each individual, lcmm assigned membership probabilities for each class, and the class with the highest probability was selected as the latent class for that individual. To improve convergence to the global maximum likelihood of the model, the analyses were repeated using different sets of random starting points (Proust-Lima et al., 2017). Data analyses were

carried out using the lcmm package (last updated on 26 June 2019) in R statistical software, version 3.6.1 (released on July 25, 2019). Further details about lcmm modeling are provided in Appendix C. The final classes of cognitive state changes were also reviewed by a geriatrician for clinical validation.

Comparing results from the clinically-driven approach and the statistical modeling (lcmm) method

To determine whether the two methods produced similar classes, the classes identified using the clinically-driven approach were compared with classes identified using the lcmm approach. This comparison was performed based on the number of classes, the cognitive states experienced within each class, whether those with and without reverse transition were assigned to separate classes, and whether those who did or did not develop dementia were assigned to separate classes. A visual representation of cognitive state changes for each of the classes is presented so as to provide information on approximate timing and rates of cognitive change and to facilitate the comparison of classes of cognitive state changes identified by the clinically-driven approach with those from the statistical modeling approach (Figure 4-2 and Figure 4-3; for more details, see Appendix D, Figure D-1 and Appendix E, Figure E-1).

4.2.4 Ethics

Ethics approval by institutional review boards was obtained from the University of Kentucky for the original Nun Study and from the University of Waterloo for the current study (Office of Research Ethics number 20174).

4.3 Results

4.3.1 Sample characteristics at baseline

Table 4-1 illustrates the main characteristics of the analytic sample. The Nun Study participants were highly educated, with more than 85% having a university degree.

Table 4-1 Characteristics of participants with longitudinal cognitive assessments (N = 574)

Variables	Mean (SD)	Frequency (%)
Age (years)		
Age at first cognitive assessment	82.82 (5.16)	
Age at last cognitive assessment	90.12 (5.35)	
Education		
≤ High school		83 (14.46)
Bachelor's degree		235 (40.94)
≥ Master's degree		256 (44.60)

Abbreviation: SD = standard deviation

4.3.2 Patterns of cognitive state changes

The patterns of cognitive state changes that were identified using the clinically-driven approach and the statistical modeling approach (lcmm) are presented below.

4.3.2.1 Patterns of cognitive state changes identified based on the clinically-driven approach

Using the clinically-driven approach, seven patterns of cognitive state changes were identified. These included three with stable cognitive states (normal cognition [N = 28, 5%],

MCI or GI [N = 71, 12%], and dementia [N = 87, 15%]), and four with cognitive state transitions. Patterns with reverse transition(s) to better cognitive states included reversion without developing dementia (N = 143, 25%) and with eventual transition to dementia (N = 37, 6%). Two patterns featured progressive cognitive decline that either did not (N = 77, 14%) or did (N = 131, 23%) lead to dementia. Trajectories of cognitive state changes for the first six individuals within each of these seven patterns are presented in Figure 4-2. (All trajectories of cognitive state changes for the seven patterns are presented in Appendix D, Figure D-1.) In Figure 4-2, the seven rows represent patterns with: 1) stable normal cognition, 2) stable MCI or GI, 3) decline and improvement without dementia, 4) progressive decline without dementia, 5) decline and improvement with eventual progression to dementia, 6) progressive decline with eventual progression to dementia, and 7) stable dementia.

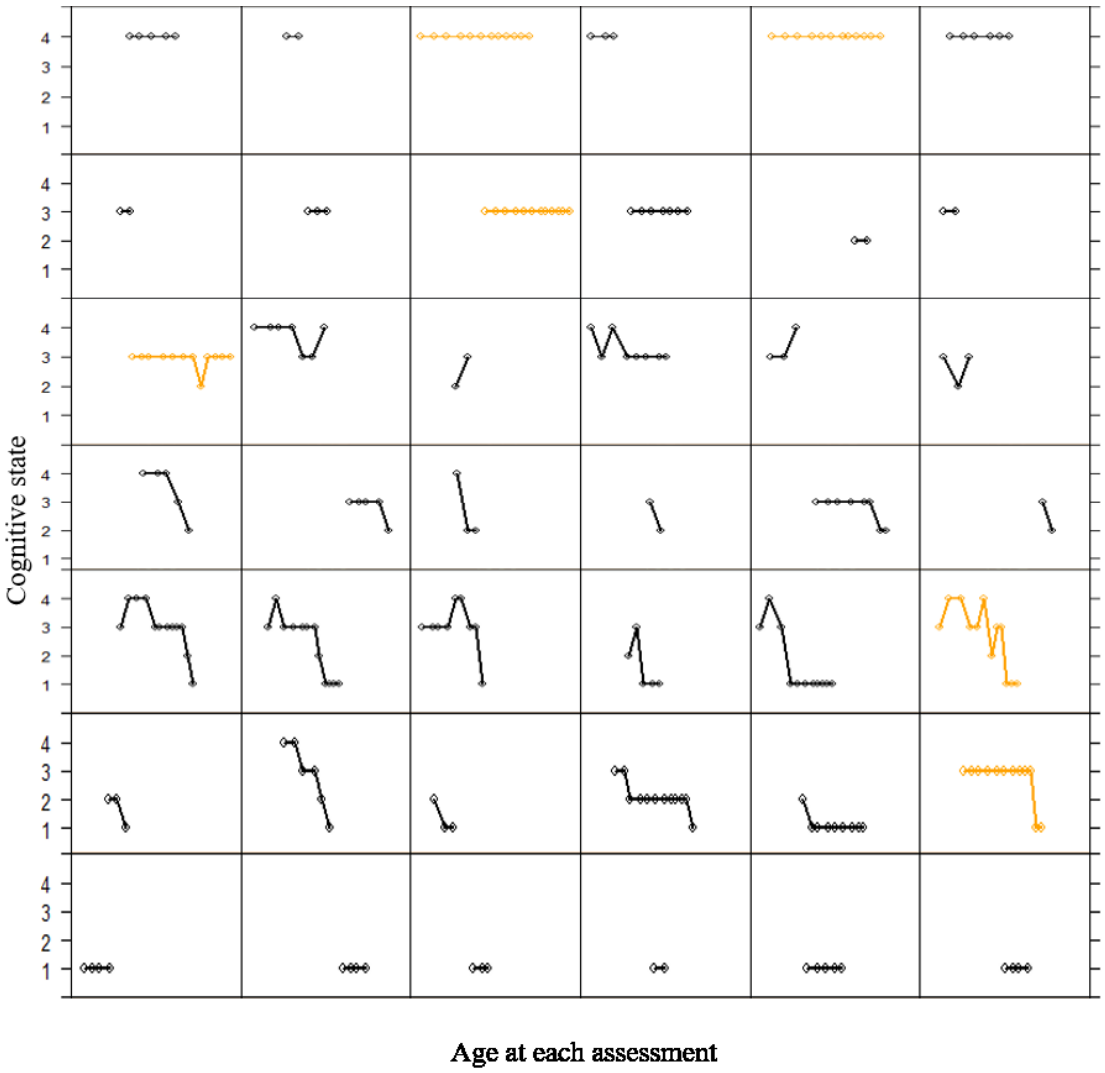

Figure 4-2 The first six observed trajectories from each of the seven patterns of cognitive state changes identified using the clinically-driven approach (overall sample N = 574)

From top to bottom: Pattern 1) Stable normal cognition, Pattern 2) Stable mild or global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with eventual progression to dementia, Pattern 6) progressive decline with eventual progression to dementia, and Pattern 7) stable dementia; black trajectories represent participants who died before the end of the data collection period; orange trajectories represent participants who remained alive until the end of the data collection; cognitive states: 4 = normal cognition, 3 = mild cognitive impairment, 2 = global impairment, and 1 = dementia

4.3.2.2 Classes of cognitive state changes identified based on the statistical modeling method

The lcmm model with random intercept, age, age squared, and four latent classes had the smallest BIC, reasonable average posterior probabilities, and clinically meaningful distinct classes of cognitive state changes. The decrease in BIC from the model with four latent classes to the model with five classes was minor (change in BIC < 3). Therefore, the model with four latent classes was investigated as a potential best fit to distinguish distinct classes of cognitive state changes. The posterior probabilities for the model with four latent classes were all above 0.7 and the trajectories within each class were more similar than the trajectories within the other three classes. Therefore, the model with four latent classes was selected as the best fit to identify distinct classes of cognitive state changes. A random slope for cognitive trajectories over time within each latent class was also added to the model to account for any potential between-participant heterogeneity of change in four levels of cognitive states over time. However, the fit for this model was poorer than the model without a random slope. Therefore, the final model did not contain a random slope parameter. For comparison, the fitting criteria for models with a random intercept, age, and age squared, and different numbers of latent classes is presented in Table 4-2, and the corresponding distribution of participants within each class is shown in Table 4-3.

Trajectories of cognitive state changes for the first six individuals within each of these four classes are presented in Figure 4-3. (All trajectories of the cognitive state changes for four classes are presented in Appendix E, Figure E-1.) The participants in Class 1 experienced the healthiest patterns of cognitive state changes until death or the end of follow-up. These individuals were observed with normal cognition for several years and rarely developed dementia. Participants in Class 2 experienced lower levels of cognition than individuals in Class 1, with fewer years with normal cognition and a higher proportion who developed dementia. Compared to participants in Class 2, more participants in Class 3 developed

dementia; however, progression to dementia happened at an older age than participants in Class 4. Finally, most participants in Class 4 developed dementia at a younger age than participants in Class 3 and lived with dementia for several years.

Table 4-2 Comparison of the fitting criteria for the latent class mixed-effects modeling approach (with a random intercept and linear and quadratic terms for age) with different numbers of latent classes based on Bayesian information criterion (BIC) and average posterior probability in each class (N=574)

				Average Posterior probability				
Number of classes	**Number of parameters**	**log-Likelihood**	**BIC**	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**
1	6	-3258.27	6554.66	1				
2	10	-3108.55	6280.63	0.82	0.86			
3	14	-3047.27	6183.47	0.85	0.76	0.79		
4	18	-3014.61	6143.57	0.82	0.73	0.78	0.72	
5	22	-3003.13	6146.02	0.83	0.72	0.74	0.72	0.68

Abbreviation: BIC = Bayesian information criterion

Table 4-3 Comparison of the distribution of participants in each class for models with different numbers of latent classes based on the latent class mixed-effects modeling approach with a random intercept and linear and quadratic terms for age (N=574)

	Number (%) per latent class				
Number of classes	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**
1	574 (100%)				
2	253 (44.08%)	321 (55.92%)			
3	1536 (27.18%)	194 (33.80%)	224 (39.02%)		
4	73 (12.72%)	100 (17.42%)	210 (36.59%)	191 (33.28%)	
5	72 (12.54%)	93 (16.20%)	166 (28.92%)	218 (37.98%)	25 (4.26%)

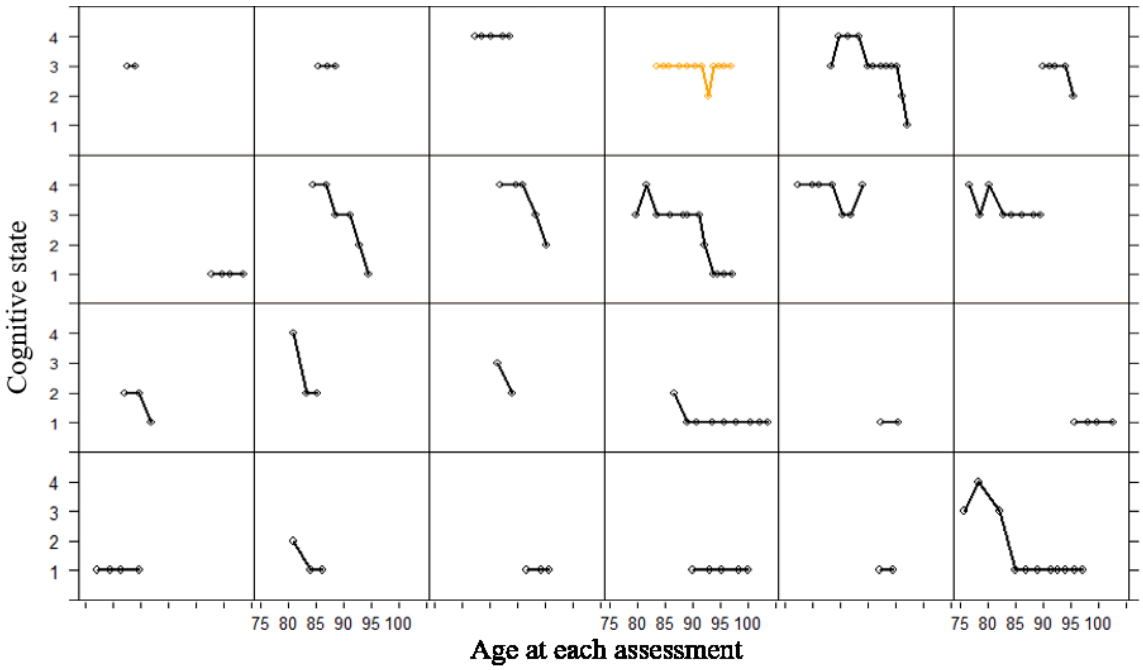

Figure 4-3 The first six observed trajectories from each of the four classes of cognitive state changes identified using the latent class mixed-effects modeling approach (overall sample N = 574)

From top to bottom, Class 1 represents the healthiest trajectories of cognitive state changes and Class 4 represents the least healthy trajectories of cognitive state changes; black trajectories represent participants who died before the end of the data collection; orange trajectories represent participants who remained alive until the end of the data collection; cognitive state 4 = normal cognition, 3 = mild cognitive impairment, 2 = global impairment, and 1 = dementia

4.3.2.3 Comparing patterns of cognitive state changes identified using two different approaches

The distribution of individuals within patterns of cognitive state changes identified using the two methods is presented in Table 4-4. The clinically-driven approach led to seven distinct patterns of cognitive state changes while the lcmm approach identified four. The classes from the clinically-driven approach distinguished individuals who experienced reversion from those who did not, and also distinguished individuals who developed dementia from those who did not. The latent classes from lcmm could be logically ordered by the level of cognitive ability for participants within each latent class.

Table 4-4 Distribution of individuals within patterns of cognitive state changes based on the clinically-driven approach among participants in each latent class based on the latent class mixed-effects modeling approach

Patterns of cognitive state changes based on the clinically-driven approach	Classes of cognitive state changes based on lcmm[1]				
	Class 1	Class 2	Class 3	Class 4	Total
1) Stable normal	16	12	0	0	28
2) Stable MCI or GI	55	15	1	0	71
3) Decline and improvement, no dementia	102	38	3	0	143
4) Progressive decline, no dementia	17	43	14	3	77
5) Decline and improvement, with dementia	9	19	8	1	37
6) Progressive decline with dementia	11	56	45	19	131
7) Stable dementia	0	8	29	50	87
Total	210	191	100	73	574

[1]Latent class mixed-effects modeling with four latent classes with random intercept, and linear and quadratic terms for age, from better cognitive function (Class 1) to worse (Class 4)
Abbreviations: GI = global impairment; lcmm = latent class mixed-effects modeling; MCI = mild cognitive impairment

To further compare the distinct patterns of cognitive state changes identified in the two methods, the overall distribution of death, the years of follow-up, and the years between last assessment and death for all classes were described (Tables 4-5, 4-6, and 4-7). Within each class, the distribution of individuals by survival status at the end of the study follow-up are shown in Table 4-5. Overall, 70 out of 574 participants were alive at the end of the study follow-up. At this time, across the seven patterns of cognitive state changes identified with the clinically-driven approach, none of the participants in Pattern 7 were alive. In contrast, 32.1% of the participants in Pattern 1 remained alive. Similarly, across the four classes of cognitive state changes identified using the lcmm approach, none of the participants in the most severely impaired class (Class 4) were alive (Table 4-5).

Table 4-5 Distribution of individuals by survival status at the end of the study follow-up: (a) within patterns identified using the clinically-driven approach, and (b) within latent classes identified using the latent class mixed-effects modeling approach

(a)

Observed patterns[1] based on the clinically-driven approach								
Alive	1	2	3	4	5	6	7	Total
Yes (n)	9	8	34	7	6	6	0	70
(%)	(32.1)	(13.3)	(23.8)	(9.1)	(16.2)	(4.6)	(0.0)	(12.2)
No (n)	19	63	109	70	31	125	87	504
(%)	(67.9)	(86.7)	(76.2)	(90.9)	(83.8)	(95.4)	(100)	(87.8)
Total	28	71	143	77	37	131	87	574

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

(b)

Observed latent classes[1] based on latent class mixed-effects modeling					
Alive	1	2	3	4	Total
Yes (n)	50	18	2	0	70
(%)	(23.8)	(9.4)	(2.0)	(0)	(12.2)
No (n)	160	173	98	73	504
(%)	(76.2)	(90.6)	(98.0)	(100)	(87.8)
Total	210	191	100	73	574

[1]From better cognitive function (Class 1) to worse (Class 4)

The distribution of follow-up time and time from last assessment until death across classes is presented in Table 4-6 and Table 4-7. Participants were followed between 1.21 to 15 years. On average, participants were followed for 7.30 years (SD = 4.26), and average time from last assessment until death was 1.05 years (SD = 1.65) (Table 4-6 and Table 4-7). There is a time gap between the 3rd quartile for years from last follow-up until death and the maximum years from last follow-up until death. This longer time gap between the last assessment and death was observed for 19 individuals who were alive but missed their follow-up cognitive assessments.

Table 4-6 Distribution of (a) follow-up time and (b) time from last assessment until death in each class identified using the clinically-driven approach

(a)	Observed patterns[1] based on the clinically-driven approach							
Years of follow-up	1	2	3	4	5	6	7	Overall
Mean (SD)	7.36	4.41	9.38	7.10	10.83	7.51	4.57	7.30
	(4.75)	(3.56)	(4.12)	(4.11)	(3.30)	(3.77)	(2.72)	(4.26)
Minimum	1.29	1.21	1.60	1.28	4.39	1.23	1.53	1.21
1st quartile	2.63	1.67	6.00	3.37	8.60	4.46	2.39	3.38
Median	6.46	3.11	9.83	7.10	11.68	7.18	3.47	6.82
3rd quartile	12.13	5.64	13.42	10.11	13.94	10.89	5.76	10.94
Maximum	14.51	14.97	15.00	14.99	15.00	14.57	11.89	15.00
Total subsample	28	71	143	77	37	131	87	574

(b)								
Years from last follow-up until death	1	2	3	4	5	6	7	Overall
Mean	2.32	2.00	0.91	1.24	0.62	0.68	0.80	1.05
(SD)	(3.23)	(2.84)	(1.01)	(2.11)	(0.70)	(0.51)	(1.06)	(1.65)
Minimum	0.30	0.06	0.01	0.01	0.02	0.01	0.01	0.01
1st quartile	0.50	0.75	0.44	0.42	0.28	0.24	0.30	0.38
Median	0.90	1.07	0.68	0.64	0.47	0.59	0.71	0.70
3rd quartile	1.72	1.38	1.00	1.22	0.68	0.92	1.07	1.12
Maximum	10.14	12.43	6.67	13.39	3.82	2.15	9.43	13.39
Deceased subsample	19	63	109	70	31	125	87	504

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviation: SD = standard deviation

Table 4-7 Distribution of (a) follow-up time and (b) time from last assessment until death in each latent class identified using the latent class mixed-effects modeling approach

(a)	Observed latent classes[1] based on latent class mixed-effects modeling				
Years of follow-up	1	2	3	4	Overall
Mean (SD)	8.31 (4.51)	7.30 (4.26)	6.44 (3.73)	5.58 (3.38)	7.30 (4.26)
Minimum	1.21	1.24	1.53	1.23	1.21
1st quartile	4.29	8.13	3.12	2.89	3.38
Median	7.98	6.93	5.48	5.29	6.82
3rd quartile	13.02	11.03	10.07	7.61	10.94
Maximum	15.00	15.00	14.04	13.94	15.00
Total subsample	210	191	100	73	574

(b)

	Observed latent classes based on latent class mixed-effects modeling				
Years from last follow-up until death	1	2	3	4	Overall
Mean (SD)	1.28 (1.85)	1.06 (1.86)	0.81 (1.07)	0.85 (1.19)	1.05 (1.65)
Minimum	0.04	0.01	0.01	0.01	0.01
1st quartile	0.48	0.37	0.24	0.31	0.38
Median	0.78	0.63	0.63	0.72	0.70
3rd quartile	1.22	1.02	1.03	1.10	1.12
Maximum	12.43	13.39	9.43	9.92	13.39
Deceased subsample	160	173	98	73	504[2]

[1]From better cognitive function (Class 1) to worse (Class 4)
[2]70 participants were alive at the time of last cognitive assessment
Abbreviation: SD = standard deviation

4.4 Discussion

Using longitudinal data from the Nun Study, this study modelled cognitive aging through trajectories of change across four cognitive states: normal cognition, MCI, GI, and dementia. Individuals were grouped into distinct patterns of cognitive state changes using two methods: a clinically-driven approach and a statistical modeling approach, lcmm. Using the clinically-driven approach, trajectories of cognitive state changes in the Nun Study were clustered into seven distinct patterns. The lcmm approach identified four latent classes of cognitive state changes. The results from the clinically-driven approach were preferred for identifying distinct patterns of cognitive state changes. This preference was based on the higher level of detail in patterns captured by the clinically-driven approach compared to the latent classes identified using the lcmm approach. These details include distinguishing between trajectories with and without cognitive improvement, and with and without progression to dementia.

Substantial heterogeneity was noted in the cognitive state trajectories in this population of older adults. Both methods led to a range of more to less heathy patterns. However, the patterns from the clinically-driven approach provided more detailed information, identifying reverse transitions from MCI or GI to normal cognition and distinguishing between trajectories that led or did not lead to dementia. Based on the results from the clinically-driven approach, 25% of our sample experienced reversion and never developed dementia. Reverse transitions were from MCI or GI to normal cognition, or from GI to MCI. Only 20% of participants who experienced reverse transition(s) developed dementia, reflecting that dementia is not an inevitable cognitive state after developing MCI or even GI. This level of detail can only be captured by modeling approaches that are able to identify more than one class of cognitive changes over time and that are sensitive to distinctions between individuals based on whether they experienced reversion to a less impaired state or progression to dementia.

The types of cognitive state changes observed in this study are consistent with those previously reported. Evidence of reverse transition from cognitive impairment to normal

cognition has been noted within the Nun Study as well as other populations (Abner et al., 2012; Iraniparast et al., 2016; Koepsell & Monsell, 2012; Malek-Ahmadi, 2016). Categories of cognitive decline observed using our two analytic methods were also reported in previous studies of transitions from normal cognition to MCI and from MCI to dementia using multi-state Markov modeling (Kryscio et al., 2008; Riley et al., 2000; Tyas et al., 2007). In addition, the patterns of cognitive state changes that were identified using the clinically-driven approach expand patterns that were reported previously by Aiken-Morgan et al. (2017). They identified four patterns of cognitive state changes: 1) normal cognition, 2) stable MCI, 3) converters from normal cognition to MCI, and 4) reverters from MCI to normal cognition. No progression to dementia was observed, likely due to the short follow-up period (less than four years). However, they did confirm other reports of reversion from MCI, noting that 13% of their sample experienced improvement from MCI to normal cognition (Aiken-Morgan et al., 2017). While broadly consistent with these findings, our study expands their converter and reverter categories each to two patterns with or without progression to dementia. In addition, our study identified a pattern of stable dementia and expanded the stable MCI pattern to include GI.

Other than the study by Aiken-Morgan et al. (2017), no previous study has identified distinct patterns of change in overall cognitive states. Similar studies that have investigated patterns of change within specific domains or tests that either used (Rajan et al., 2019; Verlinden et al., 2016) or did not use (Bretsky et al., 2003; D. Mungas et al., 2010; Wilson et al., 2012; Yaffe et al., 2009) lcmm modeling have reported results similar to those from our lcmm modeling. However, these studies and our lcmm results have been unable to identify the previously reported reverse transitions from cognitive impairment to normal cognition. Therefore, the clinically-driven approach used in our study to identify distinct patterns of cognitive state changes was preferred as it was able to identify both patterns of change and patterns with progression and reversion, and also could distinguish patterns that led or did not lead to dementia.

Strengths of this study include characteristics of the underlying data from the Nun Study as well as the analytic approach. The Nun Study is a community-based sample, which provides a natural cognitive trajectory based on the study design's fixed times for cognitive assessments. This is in contrast to clinic-based samples, where assessments are often precipitated by cognitive change. In addition, the extensive longitudinal data had low levels of attrition and missing assessments, providing a robust data set for identifying patterns of cognitive state changes. Identification of two levels of cognitive impairment between normal cognition and dementia (MCI and GI) provided a more detailed perspective on cognitive trajectories than other studies, which typically have included only MCI. The homogeneity of the study participants controlled for many potential confounding factors; for example, participants were all similar in marital status, income, alcohol and tobacco use, social support, and access to healthcare.

Both analytical approaches in this study had specific strengths in identifying distinct patterns or classes of cognitive state changes in older adults. A strength of the clinically-driven approach in identifying the patterns of cognitive state changes is in providing patterns that are more likely to be conceptually and clinically meaningful than the results of statistical modeling approaches, and that can be reviewed by clinicians for face validity, as was done in this study. When applying a clinically-driven approach to identify distinct patterns of cognitive state changes, other studies may use the patterns identified in this research as a starting point; however, the applicability of these patterns to their study populations would need to be confirmed, and the potential occurrence of other types of patterns not observed in this study also recognized.

In contrast, a strength of the lcmm modeling approach is that it distinguishes groups of individuals with significantly different cognitive trajectories (latent classes), which is conceptually a meaningful addition to mixed modeling for which, in general, average trajectories are assigned to the whole sample. This statistical approach may identify these latent classes based on characteristics, or combinations of characteristics, that are not

identified in a manual review because of the complexity of combinations. In addition, the lcmm approach models the actual age at cognitive assessments rather than the assessment time planned in the study design. This modeling approach allows inclusion of participants who miss follow-up assessments and is flexible enough to model ordinal longitudinal outcomes (Proust-Lima et al., 2017). This likelihood-based approach can model data missing at random and does not require data to be missing completely at random. In the Nun Study, similar to other studies of aging and cognition among older adults, attrition due to death is present; however, death in populations of older adults does not interfere with the assumption that data are missing at random.

Comparing the results of the clinically-driven approach with the lcmm modeling allows for assessment of the performance of this statistical modeling approach in terms of its ability to identify meaningful patterns that are conceptually relevant in longitudinal studies of aging and cognition. This comparison provided knowledge on potential clinical aspects of cognitive trajectories that might be missed in the lcmm approach in contrast to potential factors (e.g., age at cognitive assessment) that cannot easily be considered in a clinically-driven approach.

Limitations of the Nun Study in identifying patterns of cognitive state changes and in predicting the patterns in other populations include characteristics of the sample, study design, and available data. The Nun Study participants are a special population who are not representative of the general population of older women in the United States, and so the results of this study need to be interpreted accordingly. Cognitive assessments were performed at specific times pre-identified by study design. Therefore, cognitive states might have changed between two observed states (interval censoring). The Nun Study participants were 75+ at baseline; cognitive trajectories at younger ages thus could not be detected and some participants were already in the dementia state at the beginning of the study [these individuals were at early stages of dementia and were intact enough to consent and participate in the study] (left censoring). Furthermore, some participants were alive at the end of data collection for this study and thus their full cognitive trajectory to death could not be

captured (right censoring). Finally, individuals who had died with dementia and individuals at severe stages of cognitive impairment due to dementia at the start of the study could not be included in this study (left truncation). However, left truncation and right censoring may cancel out the effect of each other on the overall prevalence of dementia in the Nun Study. Furthermore, experiencing improvement from cognitive impairment to normal cognition might be due to treatment of factors that led to cognitive impairment, such as thyroid problems or other treatable factors. However, data on such interventions were not available.

Limitations of the analytical approaches in this study vary by type of approach. Applying the clinically-driven method to identify an initial set of patterns was time-intensive, and the patterns identified in this study may differ in other data sets. However, now that these patterns have been identified, this clinically-driven approach can be more easily applied to other populations keeping in mind that modification might still be required due to differences across populations. The lcmm approach identified meaningful patterns of cognitive state changes; however, some details of trajectories that are clinically meaningful were not captured in the four latent classes. For example, trajectories with and without improvement to a higher cognitive level, or trajectories that led or did not lead to dementia are clinically meaningful, but were not clearly distinguished in the lcmm approach. One reason for less clear distinctions between diverse trajectories of cognitive state changes using the lcmm approach might be a low absolute fit of the model. Using BIC and the average posterior probabilities, the model with four latent classes was identified as a better fit than the models with a differing number of latent classes. The absolute fit of the model to the data set could not be tested due to the lack of available analytic approaches. However, a model with only a linear term for age was also fitted to the model and the model with both linear and quadratic terms for age created more clinically meaningful latent classes.

Membership in specific patterns of cognitive state changes is clinically meaningful as it reflects different cognitive aging patterns and subsequent needs for care, treatment, and support. By providing information on cognitive state changes over time in older adults to

guide their prognosis, and on the frequency of reversion from a more to less impaired cognitive state including normal cognition, this research will benefit older adults and their families, and the healthcare system. Given the trend to earlier intervention for prevention of dementia, these results may also improve the design of clinical trials and the interpretation of their results, given that many individuals experience reversion from MCI or GI to normal cognition even without intervention. This research has identified an alternate cognitive outcome—membership in a pattern of cognitive state changes—to study the effect of genetic, environmental, psychosocial, and lifestyle factors on cognitive aging. Knowledge of predictors of these patterns of cognitive aging may also inform population-level interventions to promote healthy aging.

In this study, patterns of cognitive state changes were identified based on one purely clinically-driven approach and one purely computational (statistical modeling) approach developed for general patterns of change in longitudinal studies. Developing a method to identify patterns of cognitive state changes that is more sensitive to reversion based on both the clinical approach and the computational method would be helpful for future research on cognitive aging.

The focus of this study was on cognitive state changes to dementia; further research on stages of dementia would provide a more comprehensive picture of cognitive trajectories. For example, a study that used lcmm approach on a sample of older adults with Alzheimer's disease identified three distinct patterns of cognitive decline (Geifman et al., 2018). In addition, future research could examine how cognitive trajectories differ among older adults based on type and timing of interventions. Given the time period over which the Nun Study population was followed in this study, interventions for cognitive impairment were limited, and thus this study provides information on the natural history of cognitive trajectories. These trajectories are relevant particularly when interventions are not possible or feasible due to financial constraints, other health conditions, or when interventions do not help to modify progression. Further research is also needed to determine the potential patterns of cognitive

aging in other populations and to identify predictors of membership in these patterns to target interventions of modifiable risk factors to support healthy cognitive trajectories.

In this research, the association of brain pathology with the patterns of cognitive state changes was not studied. For example, some participants in the pattern with progressive cognitive decline with dementia experienced rapid decline from normal cognition to dementia, which could be due to delirium or stroke. In a study of 1096 older adults with annual cognitive assessments for up to 21 years and brain donation, several pathological factors such as Alzheimer's pathology, vascular pathologies, and Lewy bodies were associated with cognitive trajectories. However, their effects of these pathologies on cognitive trajectories differed. For example, Alzheimer's pathology was associated with progressive cognitive decline, but atherosclerosis was associated with lower overall cognitive performance with a relatively stable trajectory (Boyle et al., 2017).

Overall, the trajectories of cognitive aging seen in this study were heterogeneous and included substantial proportions of older adults in trajectories reflecting cognitive improvement, even in this very old population. A possible explanation for this heterogeneity in patterns of cognitive state changes includes intellectual and genetic factors, which are studied in Chapters 5 and 6, respectively.

Chapter 5
The Association of Academic Achievement with Patterns of Cognitive State Changes

5.1 Introduction

With the global population of older adults increasing, the prevalence of age-related conditions such as dementia is also increasing across the world. In 2010, the prevalence of dementia was 36 million, and this number is expected to increase to 66 million cases by 2030 and to 115 million cases by 2050 (Ferri et al., 2005; Prince et al., 2013). Dementia is among the top ten conditions contributing to increased years lived with disability among older adults (Prince et al., 2015). On the other hand, healthy cognitive aging is associated with well-being and health-related quality of life among older adults (Davis et al., 2015).

More years of education are known to be associated with cognitive reserve—that is, when Alzheimer's pathology is present, those with higher education may not develop the clinical signs of dementia typically associated with this pathology, or may develop it later, compared to individuals with lower education (Y. Stern et al., 1999). In addition, longitudinal studies of aging and cognition have observed that higher educational attainment is associated with potential cognitive reserve as shown through four categories of evidence: 1) higher cognitive performance upon reaching older adulthood (Alley et al., 2007; McDermott et al., 2016; D. Mungas et al., 2018; Tucker-Drob et al., 2009; Wilson et al., 2019; Zahodne et al., 2015); 2) slower cognitive decline compared to older adults with lower educational attainment (Alley et al., 2007; McDermott et al., 2016; Reas et al., 2017; Zahodne et al., 2015); 3) delayed accelerated decline (when clinical diagnosis of dementia occurs at an older age for individuals with higher than with lower educational attainment, but once reserve is exhausted and decline begins, this decline is faster in those with higher educational attainment) (Castro-Costa et al., 2011; Clouston et al., 2019; Hall et al., 2007; Wattmo et al., 2014); and 4) greater probability of reversion from mild cognitive impairment (MCI) to normal cognition (Canevelli et al., 2016; Sachdev et al., 2013; Xue et al., 2019). While some of these studies

have found that higher educational attainment does not slow cognitive decline (Karlamangla et al., 2009; D. Mungas et al., 2018; Muniz-Terrera et al., 2009; Tucker-Drob et al., 2009; Wilson et al., 2019; Zahodne et al., 2011), their results cannot be interpreted as effectively contradicting the theory of cognitive reserve for the effect of education on cognitive aging because methodologic issues such as their analytic approach may have led to the observed non-significant association between higher education and slower rate of cognitive decline.

The first three categories of evidence on how educational attainment is associated with cognitive reserve among older adults modeled cognition through temporal cognitive trajectories; however, they did not identify whether individuals with higher levels of education experienced cognitive improvement (i.e., reversion to a less impaired state). On the other hand, although reversion has been investigated in the fourth category of evidence, these studies do not model temporal cognitive trajectories for individuals who experience reverse transitions, such as whether those who experience reverse transitions eventually develop dementia.

Our previous work on patterns of cognitive state changes among older adults addressed these gaps by combining both temporality and reversion (see Chapter 4) and sets the stage to examine predictors of these patterns. In addition, little is known about the impact of measures of academic achievement beyond education on late-life cognition. The aim of this study was to identify the association of academic achievement (educational attainment and academic performance) with temporal patterns of cognitive state changes.

5.2 Methods

5.2.1 Sample

This study is based on secondary data from the Nun Study, a longitudinal cohort study of aging and cognition. The participants are American members of a religious congregation, the School Sisters of Notre Dame. Between 1991 and 1993, all members who were 75 years or older and living in communities in the midwestern, eastern, and southern United States were

invited to join the Nun Study (N=1,031), and 678 (66%) volunteered to participate. These volunteers did not differ significantly from nonparticipants in their average age at baseline, mortality rate, race, and country of birth (Snowdon et al., 1996).

Individuals needed to have at least one follow-up after their baseline assessment to be included in the longitudinal data analysis (n=574) (Figure 5-1). More than 87% (n = 504) of the participants were followed until death. The remaining 70 individuals were alive at the end of the assessment period, and thus their complete cognitive trajectories until death were not observed.

The sample was further restricted to exclude those with missing data on *APOE* status (n = 31) (Figure 5-1). Different subsamples of the remaining 543 individuals had complete data on academic performance in first-year high school English (n = 401), Latin (n = 368), algebra (n = 400), and geometry (n = 385). For a subsample of 411 participants, a grade was available for at least one of these four courses.

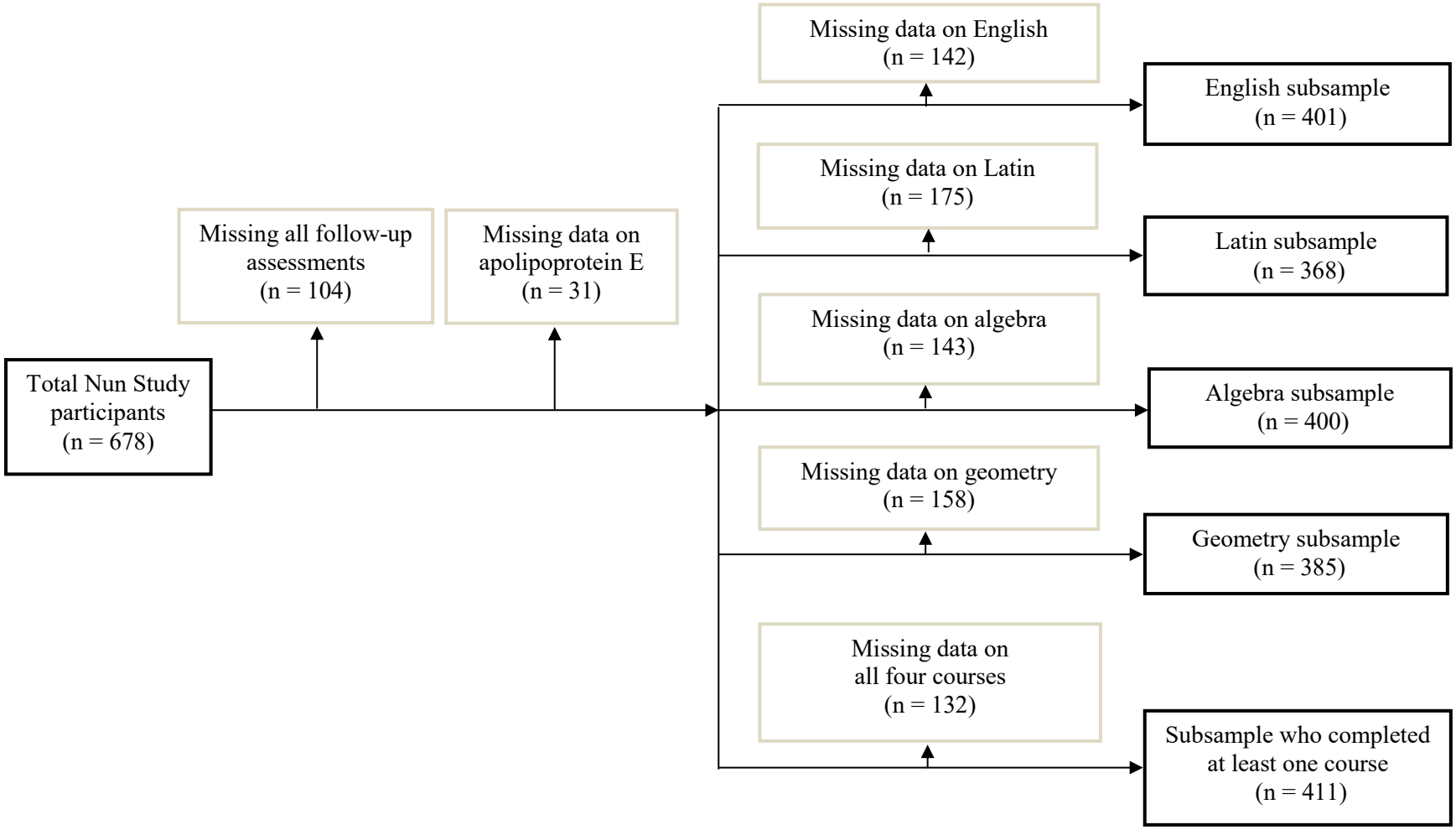

Figure 5-1 Derivation of analytic sample for testing the association of academic achievement with patterns of cognitive state changes

5.2.2 Measures

Data sources from young adulthood, middle adulthood, and late life and death were available from archival records, annual cognitive and physical assessments, and genotyping.

5.2.2.1 Exposure factors

The convent archives provided a source of early-life data, including measures of academic achievement such as overall educational attainment and academic performance in high school. Highest level of education attained was categorized as grade school, high school, Bachelor's degree, and Master's degree or higher. Final grades for the four most common courses (English, Latin, algebra, and geometry) were extracted from high school transcripts. For participants whose transcripts were available (n=411), missing grades reflect that the participant did not take that course in high school (Figure 5-1). Academic performance in each of the high school courses was treated as a continuous variable with a possible range of 0 to 100%, and was coded to determine the effect of each 10% increase in the final grade (i.e., from 70% to 80%) on patterns of cognitive state changes later in life. Overall academic performance was measured based on an average of the grades available for one or more of the four courses (grade point average [GPA]).

5.2.2.2 Outcome

The longitudinal data on cognitive states were used to identify the patterns of cognitive state changes. These longitudinal data were based on approximately annual cognitive assessments from 1991 until death or the end of the 12th round of assessments. Surviving participants at each assessment were assigned into four mutually exclusive cognitive states: 1) normal cognition; 2) MCI; 3) global impairment (GI); or 4) dementia. These assessments over time produce a sequence of longitudinal ordinal outcomes for each participant that we call a *cognitive trajectory*. The criteria assigning individuals to these cognitive states have been described previously (Riley et al., 2002; Snowdon et al., 1996; Tyas et al., 2007) and are summarized briefly below and also in Appendix A, Table A-1 (see also Chapter 4, section 4.2.2).

Normal cognition. Participants with normal cognition had intact cognition in four cognitive tests (Riley et al., 2002) in the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (≥14 for Boston Naming, ≥12 for Verbal Fluency, ≥5 for Delayed Word Recall, and ≥9 for Constructional Praxis) (Morris et al., 1989; Welsh et al., 1994), intact global cognition based on the MMSE (≥24) (Folstein et al., 1975), and intact function in at least four out of five performance-based ADL (i.e., feeding, dressing, walking, standing [transferring], and toileting) (Kuriansky & Gurland, 1976; Potvin et al., 1972).

Mild cognitive impairment. Participants with MCI were diagnosed based on having at least one specific area of impaired cognition (e.g., memory or naming) based on four cognitive tests from the CERAD neuropsychological battery, but with intact global cognition based on the MMSE (≥24), intact function in at least four out of five performance-based ADL, and not meeting criteria for dementia (Kuriansky & Gurland, 1976; Potvin et al., 1972). The cut-off point used for impairment in each test was 1.5 standard deviations below age-appropriate means, consistent with established definitions (Petersen et al., 1997; Petersen et al., 1999; Petersen, 2011; Smith et al., 1996).

Global impairment. Participants with GI were diagnosed based on having impairment in global cognitive function (MMSE < 24), in performance-based ADL, or both. They were also impaired in at least one out of four tests from the CERAD neuropsychological battery. However, participants with GI did not meet criteria for dementia because if they had impairment in two areas of cognition, they were intact for performance-based ADL (≥4) (Riley et al., 2002; Riley et al., 2005).

Dementia. For a diagnosis of dementia, a participant had to have an impairment in memory and in at least one other cognitive domain based on the CERAD neuropsychological battery, impairment in performance-based ADL, and a decline from previous cognitive level (Snowdon et al., 1997). The cut-off point used for impairment in each test was identified

using scores below the 5th percentile of age norms in the CERAD battery (Morris et al., 1989; Welsh et al., 1994).

5.2.2.3 Covariates

Age at each cognitive assessment was calculated by subtracting the birth date from the assessment date. *APOE* status of the participants was identified using genetic material from buccal cells collected from living individuals or from cadaveric brain specimens using methods described previously (Mortimer, Snowdon, & Markesbery, 2009; Saunders et al., 1996). Participants with at least one ε4 allele were classified as *APOE*-ε4 carriers.

5.2.3 Analysis

Participants were assigned to one of the seven patterns of cognitive state changes using a clinically-driven approach, with details on the grouping procedure described previously (Chapter 4, Section 4.2.3). In brief, these patterns were defined based on whether individuals experienced stable or non-stable trajectories and, among non-stable trajectories, whether they experienced a reverse transition to a less impaired state, whether they developed dementia, or both.

For bivariate analysis, the average of each continuous covariate was compared across the seven patterns using analysis of variance (ANOVA) and, when the assumptions for ANOVA—equality of variances or normal distribution for residuals—were not observed, using Kruskal-Wallis rank sum testing. For categorical covariates, the proportion of observations was compared across the seven patterns using a chi-square test. When more than 20% of cells in the contingency table had expected frequencies of less than 5, multinomial logistic bias reduction regression modeling of that categorical variable alone was used as Fisher's exact test did not converge given the extensive possible combinations of predictors with the seven outcome levels (Kim, 2017; I. Kosmidis & Firth, 2011; I. Kosmidis, 2017).

Multinomial logistic bias reduction regression modeling (I. Kosmidis & Firth, 2011) was applied to identify the association between academic achievement and membership in patterns of cognitive state changes, with membership in the most impaired pattern (stable dementia) used as the reference category. Regular multinomial logistic regression (without bias reduction) could not estimate the odds ratio and its corresponding 95% confidence interval for the association between educational attainment and membership in Pattern 1 versus Pattern 7 due to sparsity issues; specifically, there was no one with high school or lower educational attainment in Pattern 1. Multinomial logistic bias reduction regression modeling extends Firth regression (Firth, 1993) for reduced-bias estimation in full exponential family models using a computationally efficient approach (I. Kosmidis & Firth, 2011). This updated model can estimate odds ratios and their corresponding confidence intervals for all levels of exposure even when some levels of exposure have zero observations in some levels of the outcome variable. Goodness of fit for the multinomial logistic regression models was tested using the Hosmer-Lemeshow test (Fagerland, Hosmer, & Bofin, 2008).

All analyses were performed using the statistical software package R (version 3.6.1). For the bivariate analyses, ANOVA was performed using the *aov* function, the Kruskal-Wallis rank sum testing was performed using the *kruskal.test* function, and the chi-square test was performed using the *chisq.test* function. The *brmultinom* function from the *brglm2* package (I. Kosmidis, Pagui, & Sartori, 2018) was used for fitting multinomial logistic regression models with bias reduction analyses; the *logitgof* function from the *generalhoslem* package was used for checking the goodness of fit of these models (Jay, 2019).

5.2.4 Ethics

Ethics approval by institutional review boards was obtained from the University of Kentucky for the original Nun Study and from the University of Waterloo for the current study (Office of Research Ethics number 20174).

5.3 Results

Baseline mean age, *APOE*-ε4 status and educational attainment differed significantly among participants across the seven patterns of cognitive state changes (Table 5-1). Participants in Pattern 1 and Pattern 7 were the youngest and oldest individuals respectively. Participants who experienced cognitive decline and improvement without dementia (Pattern 3) had the lowest proportion of *APOE*-ε4 carriers followed by participants who experienced stable normal cognition (Pattern 1) and participants who experienced cognitive decline and improvement with eventual progression to dementia (Pattern 5).

Overall, more than 85% of the Nun Study participants had completed postsecondary education. All participants who experienced stable normal cognition (Pattern 1) had postsecondary education, and more than 80% had earned a graduate degree, the highest percentage of any of the patterns. Graduate-level education was also the most common level of education for participants who experienced reverse transitions to higher cognitive levels (Patterns 3 and 5). Similarly, the proportion of participants with graduate education was lowest for those with stable dementia (Pattern 7). The average grades in each course and the overall GPA did not differ significantly across patterns of cognitive state changes within any of the subsamples (see Table 5-1 for GPA subsample and Appendix F, Tables F-1 to F-5 for additional tables for subsamples for individual courses and for GPA).

Table 5-1 Characteristics of participants within patterns of cognitive state changes (N = 411)

	Patterns[1] of cognitive state changes							
Characteristics	1	2	3	4	5	6	7	Total
Mean age, years (SD)	78.32 (1.91)	83.16 (4.73)	80.97 (4.32)	81.99 (4.36)	82.91 (5.68)	83.55 (5.16)	86.13 (5.40)***	82.64 (5.09)
APOE-ε4 allele, n (%)								
Present	2 (10.53)	7 (20.00)	11 (9.82)	14 (23.73)	5 (16.13)	31 (30.69)	19 (35.19)	89 (21.65)
Absent	17 (89.47)	28 (80.00)	101 (90.18)	45 (76.27)	26 (83.87)	70 (69.31)	35 (64.81)**	322 (78.35)
Education, n (%)								
≤ High school	0 (0.00)	1 (2.86)	4 (3.57)	1 (1.69)	2 (6.45)	7 (6.93)	9 (16.67)	24 (5.84)
Bachelor's degree	3 (15.79)	18 (51.43)	45 (40.18)	29 (49.15)	14 (45.16)	50 (49.50)	32 (59.26)	191 (46.47)
≥ Master's degree	16 (84.21)	16 (45.71)	63 (56.25)	289 (49.15)	15 (48.39)	44 (43.56)	13 (24.07)*	196 (47.69)
Academic performance								
GPA, mean (SD)	86.35 (6.75)	88.25 (5.70)	86.97 (6.63)	88.38 (5.46)	86.18 (5.62)	86.14 (6.37)	85.88 (6.35)	86.85 (6.25)
Total sample	19	35	112	59	31	101	54	411
Deceased, n (%)	13 (68.42)	33 (94.29)	87 (77.68)	54 (91.53)	25 (80.65)	98 (97.03)	54 (100)	364 (88.56)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; GPA = grade point average; SD = standard deviation

*p < 0.05; **p < 0.01; ***p < 0.001

Adjusting for age and *APOE*, higher levels of education (Master's degree or higher) were associated with higher odds of experiencing three healthier patterns of cognitive state changes (Patterns 3, 4 [cognitive decline without dementia], or 6 [delayed onset for those who developed dementia]) versus the reference category of stable dementia (Pattern 7) (Table 5-2). These associations were slightly different for the subsample with available grades for English, algebra, and geometry, where attaining a graduate degree was associated with experiencing Patterns 3 or 4 versus stable dementia (Appendix G, Tables G-1, G-3, and G-4) and very different for the subsample with available grades for Latin, where higher educational attainment was not associated with experiencing healthier patterns (Appendix G, Table G-2). In addition, in these fully adjusted models, the covariates age and *APOE* were significantly associated with cognitive state patterns. Compared to the reference category of stable dementia (Pattern 7), older age was associated with lower odds of experiencing healthier patterns of cognitive state changes (Patterns 1, 3,4, 5, or 6) while carrying an *APOE*-ε4 allele was associated with lower odds of experiencing Patterns 1, 2, 3, 4, or 5 (Table 5-2).

In models of academic performance adjusted for age and *APOE*, each additional 10% increase in GPA was significantly associated with higher odds of experiencing the patterns of stable MCI or GI (Pattern 2) or progressive decline without dementia (Pattern 4) versus the pattern of stable dementia (Pattern 7) (Table 5-3). This association between GPA and patterns of cognitive state changes was mostly due to the association with performance in algebra: after repeating analyses for the four courses individually, only higher performance in algebra was significantly associated with experiencing Patterns 2 or 4 versus Pattern 7, with this significant association not observed for other courses (Appendix H, Tables H-1 to H-4).

In addition, in the fully adjusted model, the covariates age and *APOE* were significantly associated with cognitive state patterns. Compared to the reference category of stable dementia (Pattern 7), older age was associated with lower odds of experiencing all healthier patterns of cognitive state changes (Patterns 1, 2, 3,4, 5, or 6) and carrying an *APOE*-ε4 allele was associated with lower odds of experiencing Patterns 1, 3, or 5 (Table 5-3). Overall, the goodness of fit for all models was not rejected.

Table 5-2 The association of educational attainment with membership in patterns of cognitive state changes (N = 411)

	Pattern[1] 1 vs 7	Pattern 2 vs 7	Pattern 3 vs 7	Pattern 4 vs 7	Pattern 5 vs 7	Pattern 6 vs 7
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Unadjusted						
Education (vs. ≤ high school)						
Bachelor's degree	2.05 (0.08–52.31)	3.61 (0.52–24.87)	2.96 (0.82–10.67)	5.75 (0.85–38.85)	1.70 (0.34–8.54)	1.97 (0.64–6.02)
≥ Master's degree	**23.22 (1.02–530.91)**	**7.74 (1.07–56.12)**	**9.93 (2.06–37.88)**	**13.84 (1.96–97.71)**	4.36 (0.83–23.02)	**4.18 (1.26–13.79)**
Adjusted for age and *APOE*						
Education (vs. ≤ high school)						
Bachelor's degree	3.10 (0.10–95.56)	3.68 (0.53–25.61)	3.26 (0.80–13.33)	5.76 (0.82–40.66)	1.76 (0.34–9.08)	1.92 (0.61–6.02)
≥ Master's degree	19.81 (0.71–551.79)	6.81 (0.91–50.94)	**7.89 (1.81–34.45)**	**10.69 (1.43–79.80)**	3.85 (0.69–21.41)	**3.53 (1.02–12.27)**
Age (years)	**0.64 (0.52–0.78)**	0.91 (0.84–1.00)	**0.82 (0.76–0.89)**	**0.87 (0.80–0.94)**	**0.91 (0.83–0.99)**	**0.93 (0.87–0.99)**
APOE-ε4 carrier (vs. non-carrier)	**0.15 (0.03–0.68)**	**0.34 (0.12–0.95)**	**0.13 (0.05–0.32)**	**0.39 (0.16–0.93)**	**0.27 (0.09–0.82)**	0.61 (0.29–1.29)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; OR = odds ratio

Table 5-3 The association of average performance in four high school courses with membership in patterns of cognitive state changes (N = 411)

	Pattern[1] 1 vs 7	**Pattern 2 vs 7**	**Pattern 3 vs 7**	**Pattern 4 vs 7**	**Pattern 5 vs 7**	**Pattern 6 vs 7**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Unadjusted						
GPA[2]	1.10 (0.49–2.48)	1.85 (0.91–3.76)	1.31 (0.79–2.20)	**1.94 (1.05–3.58)**	1.07 (0.54–2.12)	1.07 (0.64–1.79)
Adjusted for age and *APOE*						
GPA	1.41 (0.60–3.28)	**2.12 (1.02–4.41)**	1.58 (0.90–2.78)	**2.29 (1.20–4.36)**	1.23 (0.60–2.51)	1.20 (0.70–2.07)
Age at first assessment (years)	**0.61 (0.50–0.75)**	**0.89 (0.82–0.96)**	**0.80 (0.74–0.86)**	**0.84 (0.78–0.91)**	**0.88 (0.81–0.96)**	**0.91 (0.86–0.97)**
APOE-ε4 carrier (vs. non-carrier)	**0.17 (0.04–0.75)**	0.38 (0.14–1.05)	**0.15 (0.06-0.36)**	0.44 (0.18–1.04)	**0.29 (0.10–0.90)**	0.67 (0.32–1.39)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

[2]categorization of overall academic performance across up to four courses measured in 10% categories

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; GPA = grade point average; OR = odds ratio

5.4 Discussion

Higher academic achievement, as evidenced by educational attainment or performance in high school courses, is associated with cognitive reserve. Adjusting for age and *APOE*, higher education (i.e., a graduate degree) was associated with patterns of cognitive decline without dementia (with or without reversion to a higher cognitive level) or delayed onset of dementia. Higher overall academic performance was significantly associated with experiencing stable cognitive impairment or cognitive impairment without dementia. This association between higher overall academic performance and healthier patterns of cognitive state changes was mostly due to the significant association with higher performance in algebra. Adjusting for academic achievement, younger age and absence of an *APOE*-ε4 allele were significantly associated with experiencing healthier patterns of cognitive state changes.

The results of this study suggest that academic achievement can contribute to cognitive reserve through four categories of evidence: 1) better cognitive performance upon reaching older age; 2) slower rate of cognitive decline; 3) delayed onset of dementia or delayed accelerated decline; and 4) reversion from a more to less impaired cognitive state.

First, this study found that adjusting for age, higher academic achievement increased the odds of experiencing patterns of cognitive state changes (Patterns 2, 3, 4, and 6) without dementia at baseline (75+ years) and thus reflected a higher cognitive level upon reaching older age than the pattern of stable dementia (Pattern 7), where individuals already had dementia at baseline. This finding is consistent with previous research that found higher educational attainment was associated with better cognitive performance upon reaching adulthood or older age (Alley et al., 2007; McDermott et al., 2016; D. Mungas et al., 2018; Y. Stern et al., 2018; Tucker-Drob et al., 2009; Wilson et al., 2019; Zahodne et al., 2015).

Second, this study also found that adjusting for age, higher academic achievement increased the odds of experiencing three distinct patterns of cognitive state changes (Patterns 2, 3, and 4) that did not lead to dementia compared to the reference pattern of stable dementia. Therefore, individuals in these three patterns had a slower cognitive decline that did not end up progressing to dementia. An effect of higher education on slower rates of

cognitive decline has also been reported previously (Alley et al., 2007; McDermott et al., 2016; Reas et al., 2017; Zahodne et al., 2015).

Third, for those individuals who did progress to dementia, higher educational attainment was found to increase the odds of experiencing a pattern with fewer years with dementia (Pattern 6) versus more years with dementia (Pattern 7) after adjusting for age, reflecting delayed onset of dementia. In addition, higher academic achievement that increased the odds of experiencing trajectories of cognitive decline without dementia (Patterns 2, 3, or 4) versus the pattern of stable dementia may reflect even longer delays to onset of dementia leading to cognitive impairment that did not progress to dementia by the time of death. Similar effects of delays in progressive cognitive decline were observed in previous research through delayed accelerated decline (Clouston et al., 2019; Hall et al., 2007; Y. Stern et al., 2018).

Fourth, higher educational attainment distinguished membership in a pattern of cognitive decline and improvement (Pattern 3) from a pattern of stable dementia (Pattern 7). This supports previous research that higher educational attainment builds cognitive reserve that may lead to reverse transitions from MCI to normal cognition (Canevelli et al., 2016; Sachdev et al., 2013; Xue et al., 2019). Sachdev et al., (2013) observed that reverters had on average one more year of education than non-reverters (12.3 vs. 11.2 years), consistent with our findings. In their sample, however, the average level of education was lower than that of the Nun Study. Our study showed beneficial cognitive outcomes for a more highly educated cohort, which may be more typical of future aging cohorts.

In addition to this evidence linking reversion to cognitive reserve, a higher level of reserve would be present if individuals with higher educational attainment had higher odds of experiencing stable normal cognition versus stable dementia (i.e., remaining in the normal cognitive state rather than experiencing MCI and then improving to normal cognition). However, in this study, higher educational attainment was not significantly associated with higher odds of experiencing the pattern of stable normal cognition than that of stable dementia. This may be because the level of reserve conferred by higher educational attainment does not completely prevent cognitive impairment. It may also reflect a statistical

power issue as all individuals with stable normal cognition had a university degree and small cell sizes across all levels of education among participants with stable normal cognition meant that there was reduced precision of estimates and less power to detect a significant association. Among those showing a stable normal cognition pattern, the younger average age and higher proportion of individuals who remained alive at the end of the data collection may also have contributed to the lack of a significant association, as their cognitive trajectories could have eventually changed if they were followed until death. In contrast, the observed association between educational attainment and patterns of cognitive state changes in this study cannot be due to higher income among those with higher education, as has been noted by others (Zahodne et al., 2015), because Nun Study participants are homogeneous with respect to income: they do not support themselves through individual incomes but instead are supported by the religious order.

Algebra was the only course where higher performance increased the odds of experiencing healthier patterns of cognitive state changes versus stable dementia. This association may reflect a specific connection of math abilities with cognitive reserve, as has been previously reported (Arcara et al., 2017). Our study suggests that an association between math abilities and cognitive reserve might vary by type of math, and be more strongly related to abilities in algebra rather than geometry. In contrast, language abilities as measured by academic performance in English and Latin were not associated with healthier patterns of cognitive aging. However, other aspects of language ability as measured by bilingualism (Antoniou & Wright, 2017) or multilingualism (Hack, Dubin, Fernandes, Costa, & Tyas, 2019) have been shown to promote healthier cognitive aging.

In a study of individuals with MCI in the Nun Study, those with higher educational attainment and higher performance in high school English were more likely to improve from MCI to normal cognition than progress from MCI to dementia (Iraniparast et al., 2016). However, in that study the participants with stable dementia (the reference pattern of cognitive state changes in the current study) were excluded as they had already developed dementia at baseline and thus did not contribute to transitions after a diagnosis of MCI. In

addition, that study did not distinguish the two predementia cognitive states used in this study (MCI and GI) and thus improvements from GI to MCI were not modeled.

Strengths of this study include characteristics of the underlying data from the Nun Study as well as the analytic approach. The Nun Study is a community-based (as opposed to a clinic-based) sample, which provides a natural cognitive trajectory based on the study design's fixed times for cognitive assessments (vs. need-based cognitive assessments in clinical records of cognitive assessments). In addition, the extensive longitudinal data had low levels of attrition and missing assessments, providing a robust data set for identifying patterns of cognitive state changes. Identification of two levels of cognitive impairment between normal cognition and dementia (MCI and GI) provided a more detailed perspective on cognitive trajectories than other studies that typically include only MCI. Archival data on academic performance allowed investigation of less frequently studied measures of early-life academic achievement. Genotyping allowed for adjustment by *APOE* status. The homogeneity of the study participants controlled for many potential confounding factors: for example, participants were all similar in marital status, income, social support, alcohol and tobacco use, and access to healthcare.

Strengths of our analytic approach include identifying multiple patterns of cognitive state changes, thus providing an appropriate perspective for studying cognitive trajectories. A strength of the approach used to identify the patterns of cognitive state changes is that it distinguishes groups of individuals with different cognitive trajectories, which are conceptually a meaningful addition to modeling approaches that assign one average pattern to the whole sample. These patterns were determined to be preferable to an alternative set identified using latent class mixed-effects modeling (see Chapter 4). In addition, bias reduction multinomial logistic regression models were used to model the association between covariates and patterns of cognitive state changes. This analytic method is able to estimate point estimates (ORs) and their corresponding confidence intervals for all levels of exposure and outcome even when no observations were available for some categories. However, using bias reduction multinomial logistic regression to estimate associations for categories with

zero or few observations has limitations: these estimations are less meaningful and interpretable due to wide confidence intervals. The goodness of fit for all multinomial models was not rejected; however, statistically, the validity of these tests in the presence of sparse observations needs to be checked in future research.

Limitations of the Nun Study include that its participants are a special population of women with very similar lifestyles who are not representative of the general population of older women in the United States, and the results of this research need to be interpreted accordingly. On the other hand, the results of this research on the Nun Study represent the potential possibilities of healthier cognitive aging in a special population who implements many of the protective factors (e.g., high educational attainment and academic performance, and high social support) and avoids many of the risk factors (e.g., tobacco and excessive alcohol use) for healthy cognitive aging. Participants of the Nun Study are generally well educated, and their level of education is more similar to the future generation of older women than the general population of women in their birth cohort who experienced educational disadvantages (Bonaiuto et al., 1995; Launer et al., 1999). In population studies of the association between education and cognition among older adults 70 and older, the effect of education on cognitive reserve was only observed in men (Mielke, Vemuri, & Rocca, 2014). However, in the Nun Study's all-female population, a significant association between higher educational attainment and cognitive reserve was observed.

Cognitive assessments were performed at specific times, pre-identified by the study design to be approximately one year apart. Therefore, cognitive states might have changed and then reverted between two assessments and this intervening change would not have been detected. In addition, the Nun Study participants were 75+ at baseline. Therefore, cognitive trajectories before this age could not be detected, and some participants were already in the dementia state at the beginning of the study. Finally, at the end of the cognitive assessment follow-up period, 70 participants were alive and their future cognitive trajectories were not known.

Despite the limitations mentioned above, this study contributes to our understanding of healthy cognitive aging and its predictors. The implication of a broad measure of "academic

achievement" that goes beyond educational attainment and includes levels of academic performance across different subjects suggests that reaching for higher academic achievement either through higher educational attainment or academic performance may contribute to cognitive reserve and healthier cognitive aging. The significant association between high school algebra grades and pattern of cognitive state changes suggests that, beyond the overall level of education attained, the quality of performance in specific courses earlier in life may affect patterns of cognitive trajectories later in life. Higher academic achievement can contribute to building cognitive reserve through higher cognitive levels upon reaching older age, a slower rate of cognitive decline, reversion to a higher cognitive level after showing signs of impairment, and, when dementia does occur, a delay in its onset. Understanding the association between academic achievement and patterns of cognitive state changes has implications for developing strategies to build cognitive reserve and promote healthy cognitive aging.

Chapter 6

The Effect of Apolipoprotein E on Educational Attainment Earlier in Life and on Patterns of Cognitive State Changes Later in Life: Testing the Antagonistic Pleiotropy Hypothesis

6.1 Introduction

Apolipoprotein E (*APOE*) is the most significant genetic risk factor for Alzheimer's disease, the most common type of dementia. Previous research on the effect of *APOE* on cognition earlier and later in life has suggested that the *APOE*-ε4 allele may be associated with higher cognitive abilities earlier in life, but with cognitive decline and dementia later in life. In children and young adults, *APOE*-ε4 has been associated with better performance in cognitive abilities such as infant development (Wright et al., 2003), visuospatial processing (Bloss et al., 2010), verbal fluency (Marchant et al., 2010), decision making (Marchant et al., 2010), performance on neuropsychological tests (Han & Bondi, 2008), IQ scores (Yu et al., 2000), and educational attainment (Hubacek et al., 2001). However, other studies have not found this beneficial effect of *APOE*-ε4 on cognition earlier in life (Bretsky et al., 2003; O'Donoghue et al., 2018). In contrast, the adverse effect of *APOE*-ε4 on higher risk and earlier onset of Alzheimer's disease is observed consistently across studies and populations (Corder et al., 1993; Spinney, 2014). *APOE*-ε4 is also associated with an increased risk of vascular dementia (Chuang et al., 2010), all-cause dementia (Llewellyn et al., 2010), and cognitive decline among older adults without dementia (Han & Bondi, 2008).

In the field of evolutionary biology, this beneficial effect of a genetic allele earlier in life contrasted with its adverse effects later in life is termed antagonistic pleiotropy, a concept proposed in the 1950s by Medawar (1952) and Williams (1957). With increases in life expectancy of humans well beyond the reproductive period, genes with a potential antagonistic pleiotropy effect now have more time to exert their detrimental effects later in life. Therefore, studying the potential antagonistic pleiotropy effect of genes in humans is essential for public health (Byars & Voskarides, 2019). Based on previous studies that

investigated the effects of *APOE*-ε4 on cognition in separate samples of younger and older individuals, the ε4 allele of the *APOE* gene has been suggested to have an antagonistic pleiotropy effect on cognition (Alexander et al., 2007; Tuminello & Han, 2011; Wright et al., 2003).

Tuminello & Han (2011) also suggested that because there is evidence to support beneficial effects of the *APOE*-ε4 allele during childhood and young adulthood in addition to detrimental effects during older adulthood, assessing the interaction between age and *APOE*-ε4 when studying the effect of *APOE*-ε4 on cognition may be a valuable addition to investigations of antagonistic pleiotropy. However, when the effect of *APOE*-ε4 on cognition earlier in life and later in life is assessed on separate samples, as has been done in previous studies (Corder et al., 1993; Spinney, 2014; Wright et al., 2003), this interaction cannot be tested. One study that investigated the effect of *APOE*-ε4 on cognition earlier and later in life in the same cohort did not find a significant association between *APOE*-ε4 and their measure of cognitive abilities in early life (IQ). However, they reported that *APOE*-ε4 was associated with lower nonverbal cognition in old age (Luciano et al., 2009). Their analysis for the association between *APOE*-ε4 and cognition earlier and later in life thus found an interaction between age and *APOE,* when the effect of *APOE* on cognition depended on age group.

The scaffolding theory of aging and cognition (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014) is a complementary theory to the antagonistic pleiotropy theory. The scaffolding theory implies that *APOE*-ε4 carriers who had benefited from the potential positive effect of *APOE*-ε4 on cognition earlier in life may develop cognitive reserve that will compensate for the detrimental effect of *APOE*-ε4 on late-life cognition, such that their risk of dementia would be similar to *APOE*-ε4 non-carriers. Thus far, several studies have found that higher educational attainment earlier in life could modify the detrimental effect of *APOE*-ε4 on cognition later in life (Arenaza-Urquijo et al., 2015; Reas et al., 2019; Tyas et al., 2007), although this is not universally reported (Ngandu et al., 2007). It has also been suggested that such an interaction may only be present among men (Hasselgren et al., 2019). Overall, while some evidence indicates that higher education may modify the effect of

APOE-ε4 on cognition among older adults, these studies have not determined whether *APOE*-ε4 is also associated with higher educational attainment earlier in life within the same sample. Therefore, evidence is lacking on the interaction between age (i.e., early life and late life) and *APOE*, and its impact on cognition.

One reason for the importance of identifying the association between *APOE* and cognition with aging is that *APOE* is a new target for developing treatments and yet its effect on cognition with aging is unclear (Bales & Paul, 2019; Safieh et al., 2019; Uddin et al., 2019). The aim of this study was to test the antagonistic pleiotropy effect of *APOE*-ε4 on cognition by: 1) investigating the association of *APOE*-ε4 with educational attainment earlier in life; 2) investigating the association of *APOE*-ε4 with patterns of cognitive state changes later in life; and 3) determining if educational attainment modifies the association between *APOE* status and patterns of cognitive state changes later in life.

6.2 Methods

6.2.1 Sample

The details of the Nun Study and the analytic sample for cognitive trajectories are presented in the sample section of Chapter 4 (Section 4.2.1, and duplicated in the first two paragraphs below).

This research is based on secondary data from the Nun Study, a longitudinal cohort study of aging and cognition. The participants are American members of a religious congregation, the School Sisters of Notre Dame. Between 1991 and 1993, all members who were 75 years or older and living in communities in the midwestern, eastern, and southern United States were invited to join the Nun Study (N=1,031), and 678 (66%) volunteered to participate. These volunteers did not differ significantly from nonparticipants in their average age at baseline, mortality rate, race, and country of birth (Snowdon et al., 1996).

Individuals needed to have at least one follow-up cognitive assessment after their baseline assessment to be included in the longitudinal data analysis. In the Nun Study, 104 individuals

had only one cognitive assessment (92 of these 104 died within two years of their initial assessment, reflecting the relatively low loss to follow-up in this sample other than through attrition by death). More than 87% (504 out of 574) of the participants were followed up until death. The remaining 70 individuals were alive at the end of the assessment period and thus their remaining cognitive trajectories until death were not observed.

In this study, individuals who were missing data on *APOE* status were excluded. Therefore, the analytical sample for this study is 574 – 31 = 543 (Figure 6-1).

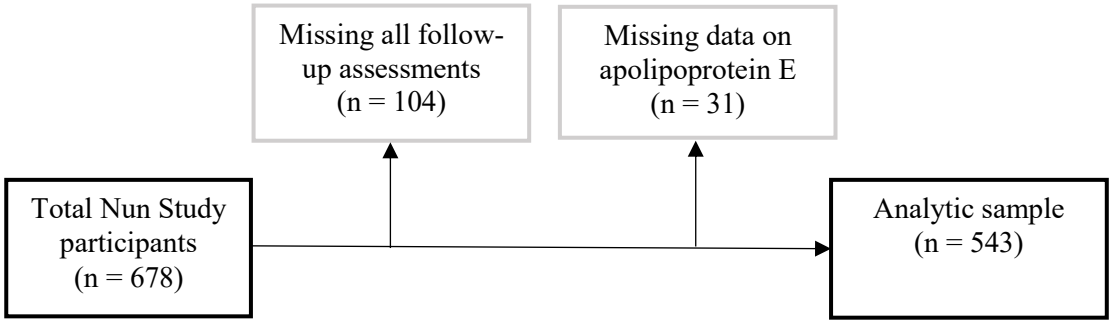

Figure 6-1 Derivation of analytic sample for testing the potential antagonistic pleiotropy effect of apolipoprotein E

6.2.2 Measures

To test whether *APOE*-ε4 has an antagonistic effect on cognition, its effect on cognitive performance both earlier and later in life must be investigated. In this study, cognitive performance earlier in life was measured by highest level of educational attainment, recorded based on four categories: grade school, high school, bachelor's degree, and master's degree or higher. Cognitive performance later in life was measured by longitudinal data on cognitive states summarized as patterns of cognitive state changes.

These longitudinal data were based on approximately annual cognitive assessments from 1991 until death or the end of the 12th round of assessments. Surviving participants at each

assessment were diagnosed with one of the four mutually exclusive cognitive states: 1) normal cognition; 2) mild cognitive impairment (MCI); 3) global impairment (GI); or 4) dementia. These assessments over time produce a sequence of longitudinal ordinal outcomes for each participant that we call a *cognitive trajectory*. The criteria for assigning individuals to these cognitive states have been described previously (Riley et al., 2002; Snowdon et al., 1996; Tyas et al., 2007) and are summarized briefly below and also in Appendix A, Table A.1 (see also Chapter 4, section 4.2.2).

Normal cognition. Participants with normal cognition had intact cognition in four cognitive tests (Riley et al., 2002) in the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (≥14 for Boston Naming, ≥12 for Verbal Fluency, ≥5 for Delayed Word Recall, and ≥9 for Constructional Praxis) (Morris et al., 1989; Welsh et al., 1994), intact global cognition based on the MMSE (≥24) (Folstein et al., 1975), and intact function in at least four out of five performance-based ADL (i.e., feeding, dressing, walking, standing [transferring], and toileting) (Kuriansky & Gurland, 1976; Potvin et al., 1972).

Mild cognitive impairment. Participants with MCI were diagnosed based on having at least one specific area of impaired cognition (e.g., memory or naming) based on four cognitive tests from the CERAD neuropsychological battery, but with intact global cognition based on the MMSE (≥24), intact function in at least four out of five performance-based ADL, and not meeting criteria for dementia (Kuriansky & Gurland, 1976; Potvin et al., 1972). The cut-off point used for impairment in each test was 1.5 standard deviations below age-appropriate

means, consistent with established definitions (Petersen et al., 1997; Petersen et al., 1999; Petersen, 2011; Smith et al., 1996).

Global impairment. Participants with GI were diagnosed based on having impairment in global cognitive function (MMSE < 24), in performance-based ADL, or both. They were also impaired in at least one out of four tests from the CERAD neuropsychological battery. However, participants with GI did not meet criteria for dementia because if they had impairment in two areas of cognition, they were intact for performance-based ADL (≥4) (Riley et al., 2002; Riley et al., 2005).

Dementia. For a diagnosis of dementia, a participant had to have an impairment in memory and in at least one other cognitive domain based on the CERAD neuropsychological battery, impairment in performance-based ADL, and a decline from previous cognitive level (Snowdon et al., 1997). The cut-off point used for impairment in each test was identified using scores below the 5th percentile of age norms in the CERAD battery (Morris et al., 1989; Welsh et al., 1994).

APOE status of the participants was identified using genetic material from buccal cells collected from living individuals or from cadaveric brain specimens using methods described previously (Mortimer et al., 2009; Saunders et al., 1996). Participants with at least one ε4 allele were classified as *APOE*-ε4 carriers. Age at each cognitive assessment was calculated by subtracting the birth date from the assessment date.

6.2.3 Analysis

The analytic approach has been described previously (see Chapter 5, Section 5.2.3). Participants were assigned to one of the seven patterns of cognitive state changes using a clinically-driven approach, with details on the grouping procedure described previously (Chapter 4, Section 4.2.3). In brief, these patterns were defined based on whether individuals experienced stable or non-stable trajectories and, among non-stable trajectories, whether they

experienced a reverse transition to a less impaired state, whether they developed dementia, or both.

For bivariate analysis, the average of each continuous covariate was compared across the seven patterns using analysis of variance (ANOVA) and, when the assumptions for ANOVA—equality of variances or normal distribution for residuals—were not observed, using Kruskal-Wallis rank sum testing. For categorical covariates, the proportion of observations was compared across the seven patterns using a chi-square test. When more than 20% of cells in the contingency table had expected frequencies of less than 5, multinomial logistic bias reduction regression modeling of that categorical variable alone was used as Fisher's exact test did not converge given the extensive possible combinations of predictors with the seven outcome levels (Kim, 2017; I. Kosmidis & Firth, 2011; I. Kosmidis, 2017).

Multinomial logistic bias reduction regression modeling (I. Kosmidis & Firth, 2011) was applied to identify the association between *APOE* status and educational attainment earlier in life. Regular multinomial logistic regression (without bias reduction) could not estimate the odds ratio and its corresponding 95% confidence interval for the association between educational attainment and membership in Pattern 1 versus Pattern 7 due to sparsity issues; specifically, there was no one with high school or lower educational attainment in Pattern 1. Multinomial logistic bias reduction regression modeling extends Firth regression (Firth, 1993) for reduced-bias estimation in full exponential family models using a computationally efficient approach (I. Kosmidis & Firth, 2011). This updated model can estimate odds ratios and their corresponding confidence intervals for all levels of exposure even when some levels of exposure have zero observations in some levels of the outcome variable.

Multinomial logistic bias reduction modeling (I. Kosmidis & Firth, 2011) was also applied to identify the association between *APOE* status and membership in patterns of cognitive state changes, with membership in the most impaired pattern (stable dementia) used as the reference category. Goodness of fit for the multinomial logistic regression models was tested using the Hosmer-Lemeshow test (Fagerland et al., 2008).

All analyses were performed using the statistical software package R (version 3.6.1). For the bivariate analyses, ANOVA was performed using the *aov* function, Kruskal-Wallis rank sum testing was performed using the *kruskal.test* function, and chi-square tests were performed using the *chisq.test* function. The *brmultinom* function from the *brglm2* package (I. Kosmidis et al., 2018) was used for fitting multinomial logistic regression models with bias reduction analyses; the *logitgof* function from the *generalhoslem* package was used for checking the goodness of fit of these models (Jay, 2019).

6.2.4 Ethics

Ethics approval by institutional review boards was obtained from the University of Kentucky for the original Nun Study and from the University of Waterloo for the current study (Office of Research Ethics number 20174).

6.3 Results

APOE-ε4 carriers were more common among participants who had a university degree (Bachelor's degree or higher) than among those with lower levels of education (22% vs. 16%). However, this association was not statistically significant in bivariate analyses (Table 6-1). In this analytic sample, the participants were on average 20.91 (SD = 4.43) years old when completing high school, 37.98 (SD = 7.29) years old when completing Bachelor's degree, and 46.42 (SD = 8.53) years old when completing Master's degree or higher.

Table 6-1 Apolipoprotein E status by level of education (N=543)

APOE-ε4	≤ High school	Bachelor's degree	≥ Master's degree	Total
Non-carrier, n (%)	65 (84.42%)	174 (77.68%)	188 (77.69)	427 (78.64)
Carrier, n (%)	12 (15.58%)	50 (22.32)	54 (22.31)[1]	116 (21.36)
Total	77	224	242	543

[1]p-value for the association between *APOE* and educational attainment = 0.68
Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4

As shown in Table 6-2, participants showed significant differences in baseline age, *APOE*-ε4 status, and educational attainment across the seven patterns of cognitive state changes. The pattern with stable dementia (Pattern 7) was characterized by older age at baseline (e.g., mean = 86.10, SD = 5.36 in Pattern 7 vs. mean = 78.42, SD = 1.97 in Pattern 1), and a higher proportion of *APOE*-ε4 carriers (e.g., 35.8% in Pattern 7 vs. 9.0% in Pattern 1), and those with lower educational attainment (e.g., 35.8% with ≤ high school in Pattern 7 vs. 0.0% in Pattern 1) compared to the other six patterns of cognitive state changes.

Table 6-2 Characteristics of participants within seven patterns of cognitive state changes (N=543)

	Pattern[1] 1	**Pattern 2**	**Pattern 3**	**Pattern 4**	**Pattern 5**	**Pattern 6**	**Pattern 7**
Characteristics	**N = 22**	**N = 60**	**N = 139**	**N = 74**	**N =37**	**N = 130**	**N = 81**
Age[2] (years), *mean* (*SD*)	78.42 (1.97)	83.42 (5.11)	80.86 (4.40)	82.46 (4.61)	83.10 (5.26)	83.72 (5.28)	86.10 (5.36)***
APOE-ε4 carrier *n (%)*							
Yes	2 (9.09)	14 (23.33)	13 (9.35)	16 (21.62)	5 (13.51)	37 (28.46)	29 (35.80)
No	20 (90.91)	46 (76.67)	126 (90.65)	58 (78.38)	32 (86.49)	93 (71.54)	52 (64.20)***
Education *n (%)*							
≤ High school	0 (0.00)	13 (21.67)	9 (6.47)	4 (5.41)	5 (13.51)	17 (13.08)	29 (35.80)
Bachelor's degree	3 (13.64)	25 (41.67)	53 (38.13)	34 (45.95)	16 (43.24)	57 (43.85)	36 (44.44)
≥ Master's degree	19 (86.36)	22 (36.67)	77 (55.40)	36 (48.65)	16 (43.24)	56 (43.08)	16 (19.75)***

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

[2]Age at first assessment

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; SD = standard deviation

*p < 0.05; **p < 0.01; ***p < 0.001

6.3.1 Apolipoprotein E and educational attainment earlier in life

The first part of assessing the potential antagonistic pleiotropy effect of *APOE*-ε4 on cognition was to test the association between *APOE* and educational attainment earlier in life. Although *APOE*-ε4 carriers had 1.5 times higher odds of attaining a university degree than high school or grade school education, this increase was not statistically significant (Table 6-3). Place of birth was considered as a potential factor that could influence the association between *APOE*-ε4 and educational attainment earlier in life when educational experiences might have been different. However, more than 98% of the participants completed their education in the United States. The results were similar in the subsample of participants who completed their education in the United States, and thus results from the full sample are presented (Table 6-3).

Table 6-3 The association between apolipoprotein E and educational attainment in multinomial logistic regression models

	Bachelor's degree vs. ≤ high school	**≥ Master's degree vs. ≤ high school**
	OR (95% CI)	OR (95% CI)
APOE-ε4 carrier (vs. non-carrier)	1.52 (0.76–3.01)	1.52 (0.77–2.99)

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; OR = odds ratio

6.3.2 Apolipoprotein E and patterns of cognitive state changes later in life

The second part of assessing the potential antagonistic pleiotropy effect of *APOE*-ε4 on cognition was to test the association between *APOE* and patterns of cognitive state changes later in life. In the unadjusted multinomial logistic bias reduction regression analysis, grade school or high school educational attainment (≤ high school) was used as the reference category. In the unadjusted analysis, *APOE*-ε4 carriers had significantly lower odds of experiencing stable normal cognition or patterns with reverse transition to a higher cognitive

level (Patterns 1, 2, or 3) than stable dementia (Pattern 7) (Table 6-4). After adjusting for age at first assessment and educational attainment, *APOE*-ε4 carriers had significantly lower odds of experiencing any other patterns of cognitive state changes (Patterns 1 to 6) than stable dementia. However, the analysis in Section 6.3.3 showed that the association between *APOE* and patterns of cognitive state changes depended on educational attainment. In addition, in the fully adjusted model, the covariates age and education were significantly associated with cognitive state patterns. Older age was associated with lower odds of experiencing healthier patterns of cognitive state changes (Patterns 1 to 6) versus stable dementia (Pattern 7), whereas higher levels of education (Master's degree or higher) were associated with higher odds of experiencing healthier patterns of cognitive state changes (Patterns 1 to 6) versus stable dementia (Pattern 7). The association for those with a Bachelor's degree was similar to that of a Master's degree or higher, reaching significance for three healthier patterns of cognitive decline (Patterns 3, 4, and 6) versus stable dementia (Pattern 7).

Table 6-4 The association between apolipoprotein E and seven patterns of cognitive state changes in multinomial logistic regression models

	Pattern[1] 1 vs 7	**Pattern 2 vs 7**	**Pattern 3 vs 7**	**Pattern 4 vs 7**	**Pattern 5 vs 7**	**Pattern 6 vs 7**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Unadjusted						
APOE-ε4 carrier (vs. non-carrier)	**0.22 (0.05–0.89)**	0.55 (0.26–1.18)	**0.19 (0.09–0.39)**	0.50 (0.25–1.03)	**0.30 (0.11–0.84)**	0.71 (0.39–1.30)
Model adjusted for age						
APOE-ε4 carrier (vs. non-carrier)	**0.16 (0.04–0.68)**	0.48 (0.23–1.04)	**0.15 (0.07–0.32)**	**0.42 (0.20–0.88)**	**0.26 (0.09–0.73)**	0.63 (0.34–1.17)
Age at first assessment	**0.63 (0.53–0.76)**	**0.91 (0.85–0.97)**	**0.80 (0.75–0.85)**	**0.87 (0.82–0.93)**	**0.90 (0.83–0.97)**	**0.92 (0.88–0.97)**
Model adjusted for education						
APOE-ε4 carrier (vs. non-carrier)	**0.14 (0.03–0.60)**	0.47 (0.22–1.02)	**0.14 (0.06–0.30)**	**0.37 (0.18–0.79)**	**0.24 (0.08–0.67)**	0.57 (0.30–1.06)
Education (vs. ≤ high school)						
Bachelor's degree	6.96 (0.33–148.62)	`1.70 (0.73–3.96)	**5.56 (2.30–13.44)**	**7.07 (2.29–21.83)**	2.89 (0.95–**8.78)**	**2.88 (1.37–6.08)**
≥ Master's degree	**93.68 (4.97–1764.11)**	**3.46 (1.36–8.84)**	**19.41 (7.50–50.25)**	**17.43 (5.31–57.22)**	**6.86 (2.11–22.29)**	**6.47 (2.80–14.94)**
Model adjusted for education and age						
APOE-ε4 carrier (vs. non-carrier)	**0.12 (0.03–0.53)**	**0.42 (0.19–0.93)**	**0.12 (0.05–0.26)**	**0.33 (0.15–0.71)**	**0.21 (0.07–0.60)**	**0.52 (0.27–0.98)**
Age at first assessment	**0.67 (0.56–0.80)**	**0.92 (0.86–0.98)**	**0.82 (0.77–0.88)**	**0.89 (0.84–0.96)**	**0.91 (0.84–0.99)**	**0.94 (0.89–0.99)**
Education (vs. ≤ high school)						
Bachelor's degree	7.33 (0.33–162.38)	1.67 (0.71–3.93)	**5.60 (2.22–14.10)**	**6.96 (2.23–21.76)**	2.84 (0.93–8.68)	**2.84 (1.34–6.02)**
≥ Master's degree	**48.44 (2.47–949.26)**	**2.78 (1.06–7.29)**	**12.34 (4.57–33.33)**	**13.02 (3.89–43.59)**	**5.37 (1.62–17.84)**	**5.46 (2.32–12.86)**

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia; Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; OR = odds ratio

6.3.3 Modification of the effect of apolipoprotein E-ε4 on cognition later in life through higher educational attainment

The third aim of this study was to test whether higher educational attainment earlier in life modified the detrimental effect of *APOE*-ε4 on cognition later in life. Due to sparse observations in some combinations of the seven levels of cognitive outcome and three levels of educational attainment, this analysis of interaction could not be performed using an interaction term even using the multinomial logistic bias reduction regression modeling. However, analysis of the association between *APOE* and patterns of cognitive state changes stratified by educational attainment showed evidence of effect modification. Among individuals with low levels of education (high school or less), *APOE*-ε4 was a significant predictor, with *APOE*-ε4 carriers showing a lower odds of experiencing healthier patterns of cognitive state changes (Patterns 1, 3, 4, and 5) versus stable dementia (Pattern 7) (Table 6-5). In contrast, among individuals who attained a Master's degree or higher, *APOE*-ε4 was only associated with lower odds of experiencing trajectories of decline and improvement without dementia (Pattern 3) versus stable dementia (Pattern 7) (Table 6-5). Furthermore, among individuals who attained a Master's degree or higher, older age was only significantly associated with lower odds of experiencing stable normal cognition (Pattern 1) (Table 6-5).

Table 6-5 The association between apolipoprotein E and seven patterns of cognitive state changes in multinomial logistic regression models stratified by educational attainment

	Pattern[1] 1 vs 7	**Pattern 2 vs 7**	**Pattern 3 vs 7**	**Pattern 4 vs 7**	**Pattern 5 vs 7**	**Pattern 6 vs 7**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Subsample with ≤ high school education						
APOE-ε4 carrier (vs. non-carrier)	**0.16 (0.04–0.68)**	0.48 (0.23–1.04)	**0.15 (0.07–0.32)**	**0.42 (0.20–0.88)**	**0.26 (0.09–0.73)**	0.63 (0.34–1.17)
Age at first assessment	**0.63 (0.53–0.76)**	**0.91 (0.85–0.97)**	**0.80 (0.75–0.85)**	**0.87 (0.82–0.93)**	**0.90 (0.83–0.97)**	**0.92 (0.88–0.97)**
Subsample with a Bachelor's degree						
APOE-ε4 carrier (vs. non-carrier)	0.12 (0.01–2.63)	0.37 (0.11–1.18)	**0.13 (0.04–0.42)**	0.38 (0.13–1.11)	**0.19 (0.04–0.89)**	**0.32 (0.12–0.83)**
Age at first assessment	**0.63 (0.45–0.89)**	**0.89 (0.80–0.98)**	**0.78 (0.71–0.86)**	**0.84 (0.76–0.92)**	**0.88 (0.78–0.99)**	**0.91 (0.84–0.99)**
Subsample with a Master's degree or higher						
APOE-ε4 carrier (vs. non-carrier)	0.23 (0.04–1.24)	0.79 (0.21–3.01)	**0.15 (0.04–0.53)**	0.41 (0.11–1.50)	0.42 (0.09–2.02)	1.14 (0.37–3.55)
Age at first assessment	**0.75 (0.60–0.94)**	1.04 (0.90–1.21)	0.89 (0.78–1.02)	1.01 (0.88–1.16)	1.04 (0.89–1.21)	1.05 (0.92–1.19)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; OR = odds ratio

6.4 Discussion

In this study, the potential antagonistic pleiotropy effect of *APOE*-ε4 on cognition was tested by answering three questions: 1) is *APOE*-ε4 associated with higher educational attainment earlier in life?; 2) is *APOE*-ε4 associated with membership in the least healthy pattern of cognition later in life; 3) Does higher education among *APOE*-ε4 carriers compensate for the detrimental effects of *APOE*-ε4 on cognition later in life? The study results did not support the first part of the antagonistic pleiotropy hypothesis for *APOE*. In contrast, they did support the second part of the hypothesis as *APOE*-ε4 carriers had lower odds than non-carriers of experiencing healthier patterns of cognitive state changes than the least healthy pattern (stable dementia). In addition, the third part of the hypothesis was supported because higher educational attainment was observed to compensate for the detrimental effect of *APOE*-ε4 on cognition later in life, consistent with the scaffolding theory of aging and cognition. Overall, as this study did not support the first part of the antagonistic pleiotropy hypothesis for *APOE*, it did not provide support that *APOE* has an antagonistic pleiotropy effect on cognition. However, attaining a Master's degree or higher compensated for the detrimental effects of both carrying an *APOE*-ε4 allele and older age on cognitive decline later in life.

The first two questions in testing the antagonistic pleiotropy effect of *APOE* on cognition can be translated to testing an interaction between *APOE* and age. In this study, the interaction between *APOE* and age was tested by stratified analysis for the association between *APOE* and cognition in the same sample at two different ages (in earlier and later life). The measure of cognition across these two time points differed, from the earlier-life measures of educational attainment to the later-life measures of cognitive state patterns. However, the two cognitive measures were related: higher educational attainment was associated with higher odds of experiencing healthier patterns of cognitive state changes. Thus, these different measures of cognition from earlier and later life may be considered comparable to a certain degree. The results of this study showed some evidence of interaction between *APOE* and cognition. No significant association was observed between *APOE* and earlier-life cognition; however, *APOE*-ε4 increased the odds of experiencing the least healthy pattern of cognition later in life.

The non-significant association between *APOE*-ε4 and higher educational attainment earlier in life observed in this study is consistent with a number of studies that have not found such beneficial effects for *APOE*-ε4 carriers (Bretsky et al., 2003; Hiekkanen, Kurki, Brandstack, Kairisto, & Tenovuo, 2009; F. Liu et al., 2010; O'Donoghue et al., 2018), although research supporting a beneficial effect of *APOE*-ε4 on early-life cognition is also frequent (Tuminello & Han, 2011). In addition, controversy exists on the neurobiological mechanism for an association between *APOE* and cognition in early life. A wide range of neuroimaging research has found that, during a memory task, *APOE*-ε4 carriers have higher brain activity than non-carriers (Filbey, Slack, Sunderland, & Cohen, 2006; Filbey, Chen, Sunderland, & Cohen, 2010; Filippini et al., 2009), which is sometimes considered as a sign of a beneficial effect of *APOE*-ε4 on early-life cognition (Mondadori et al., 2006). However, other research (Tuminello & Han, 2011), including a recent study by Hodgetts et al. (2019), has suggested that this higher brain activity in younger *APOE*-ε4 carriers may be a result of "lifespan systems vulnerability" that increases activity in areas of brain that were affected by early neuropathological signs of Alzheimer's disease (Buckner et al., 2009; de Haan, Mott, van Straaten, Scheltens, & Stam, 2012; Jagust & Mormino, 2011). While Tuminello & Han (2011) suggested that a lack of a beneficial effect of *APOE*-ε4 earlier in life constituted strong evidence against the antagonistic pleiotropy hypothesis for *APOE*, they also recommended more lifespan studies to test this hypothesis.

Although in this study *APOE*-ε4 carriers had higher odds of attaining a university degree than non-carriers, this association did not reach statistical significance. However, the non-significant association between *APOE*-ε4 and educational attainment earlier in life observed in our study may have been influenced by the high level of education in the Nun Study and the resultant limited variability in educational level. For example, more than 85% of participants attained a university degree, and this rose to 100% among participants with a pattern of stable normal cognition. Hubacek et al. (2001) observed a significantly higher proportion of *APOE*-ε4 carriers in their subsample with higher education than *APOE*-ε2 carriers. However, in their study higher education was defined as completing high school, as

compared to the Nun Study in which higher education was defined as a university degree that include graduate degrees.

In addition, some participants of the Nun Study attained their levels of education later in adulthood; therefore, studying the association between *APOE* and educational attainment earlier in life extended to middle age. As a result, their late-life cognitive reserve could also be a result of lifetime cognitive stimulation, as has been suggested (Y. Stern, 2012).

The significant association between *APOE*-ε4 and experiencing the pattern of stable dementia versus healthier patterns of cognitive state changes later in life that was observed in this study is also similar to results of biological and epidemiological studies that found an increased risk of Alzheimer's pathology and dementia among *APOE*-ε4 carriers (Chuang et al., 2010; Dickson et al., 2018; Glorioso et al., 2019; Llewellyn et al., 2010; Schmechel et al., 1993). Previous research in the Nun Study also showed that *APOE*-ε4 was associated with the risk of developing cognitive impairment and dementia (Riley et al., 2000; Tyas et al., 2007), but indicators of cognitive reserve, such as speaking four or more languages, may compensate for the detrimental effects of carrying an *APOE*-ε4 allele or older age on the hazard of developing dementia (Hack et al., 2019).

Finally, our findings that higher education reduced the detrimental effect of *APOE*-ε4 on late-life cognition have been reported previously (Arenaza-Urquijo et al., 2015; Reas et al., 2019; Tyas et al., 2007) and support the scaffolding theory of aging and cognition (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). *APOE*-ε4 carriers might thus have had higher odds of recruiting the frontal cortical regions after task-related regions of the brain developed impairments due to declines in neural structure and function in other regions of the brain in older age (Park & Reuter-Lorenz, 2009; Tuminello & Han, 2011). This transfer of the beneficial effect of higher education to late-life cognition could then lead to reverse transition to a higher cognitive level and prevention of dementia among *APOE*-ε4 carriers with higher educational attainment, with an effect equivalent to that seen in *APOE*-ε4 non-carriers.

Overall, this study did not support the first part of the antagonistic pleiotropy hypothesis; however, it supported the second part of the hypothesis for individuals with lower education. Therefore, the results of this study did not support the antagonistic pleiotropy hypothesis. On the other hand, this study supported the scaffolding theory of aging and cognition in that higher education could compensate for the detrimental effect of *APOE*-ε4 on late-life cognition.

Strengths of this study included characteristics of the underlying data from the Nun Study as well as the analytic approach. The most important strength of the Nun Study for this research is the availability of *APOE* genotyping and cognitive performance data both earlier and later in life, with later-life cognition being collected over 15 years. These data provide a unique opportunity to test the antagonistic pleiotropy effect of *APOE* on cognition within the same individuals, whereas most previous research has been conducted either on younger or older samples. Other strengths of the Nun Study are that it is a community-based (as opposed to a clinic-based) sample, which provides a natural cognitive trajectory based on the study design's fixed times for cognitive assessments (vs. need-based cognitive assessments in clinical records of cognitive assessments). In addition, the extensive longitudinal data had low levels of attrition and missing assessments, providing a robust data set for identifying patterns of cognitive state changes. Identification of two levels of cognitive impairment between normal cognition and dementia (MCI and GI) provided a more detailed perspective on cognitive trajectories than other studies that typically include only MCI.

The homogeneity of the study participants controlled for many potential confounding factors: for example, participants were all similar in marital status, income, social support, alcohol and tobacco use, and access to healthcare. Certain lifestyle factors, such as physical inactivity, high saturated fat consumption, and alcohol and tobacco use are associated with an increased risk of developing dementia especially among individuals carrying at least one *APOE*-ε4 allele (Kivipelto et al., 2008). The effect of *APOE*-ε4 on cognition is less influenced by variation in these lifestyle factors in the Nun Study than in other studies.

Strengths of our analytic approach include identifying multiple patterns of cognitive state changes, thus providing an appropriate perspective for studying cognitive trajectories. A strength of the approach used to identify the patterns of cognitive state changes is that it distinguishes groups of individuals with different cognitive trajectories, which is conceptually a meaningful addition to modeling approaches that assign one average pattern to the whole sample. These patterns were determined to be preferable to an alternative set identified using latent class mixed-effects modeling (see Chapter 4). In addition, bias reduction multinomial logistic regression models were used to model the association between covariates and patterns of cognitive state changes. This analytic method is able to estimate point estimates (ORs) and their corresponding confidence intervals for all levels of exposure and outcome even when no observations were available for some categories. However, using bias reduction multinomial logistic regression to estimate associations for categories with zero or few observations has limitations: these estimations are less meaningful and interpretable due to wide confidence intervals. The goodness of fit for all multinomial models was not rejected; however, statistically, the validity of these tests in the presence of sparse observations needs to be checked in future research.

Limitations of the Nun Study included that its participants were 75 years or older at baseline. Carrying an *APOE*-ε4 allele shifts the onset of Alzheimer's disease, the most common type of dementia, to a younger age (Spinney, 2014). Therefore, our results on the effects of *APOE*-ε4 on patterns of cognitive state changes may have been subject to survival bias. There were no data on cognitive trajectories before 75 and some participants already had dementia at the beginning of the study. In addition, those with normal cognition at the first assessment might previously have had mild or global impairment but reverted to normal cognition by the beginning of this study. These missed observations may have varied by *APOE*-ε4 status.

Nun Study participants are a special population of women who are not representative of the general population of older women in the United States, and so the results of this research need to be interpreted accordingly. For example, Nun Study participants generally had a high

level of educational attainment; however, the prevalence of dementia was similar to that of the general population (21% in the Nun Study; 20-25% in the general population) (van der Flier, Pijnenburg, Fox, & Scheltens, 2011). The homogeneity of the Nun Study participants regarding gender and other lifestyle factors also limited the ability to identify the effects of these factors on patterns of cognitive trajectories.

Cognitive assessments were performed at specific times, pre-identified by the study design. Therefore, cognitive states might have changed between two observed states. Experiencing improvement from cognitive impairment to normal cognition might be due to treatment of factors that lead to cognitive impairments, such as thyroid problems. However, data on such interventions were not available in this study.

While *APOE*-ε4 is primarily a risk factor for Alzheimer's disease and vascular dementia, in this study its effect was studied on patterns of cognitive change including all-cause dementia. Therefore, the effect of *APOE*-ε4 observed in this research questions was potentially weakened by other types of dementia. Understanding the effect of *APOE*-ε4 on a measure of cognition (educational attainment) earlier in life, and patterns of cognitive state changes later in life may lead to efforts for the prevention or delay of dementia. For example, these results will provide basic knowledge of cognitive trajectories for researchers working on gene therapies and pharmacological approaches to reduce the risk of dementia in *APOE*-ε4 carriers. Based on the results of this research, these researchers have a better understanding of the potential patterns of cognitive change for older adults based on their educational level and *APOE*-ε4 status.

The results of this research, while preliminary, suggest that higher educational attainment in *APOE*-ε4 carriers may compensate for the detrimental effect of *APOE*-ε4 on cognition later in life. Therefore, promoting and supporting higher educational attainment may contribute to cognitive reserve and healthier cognitive aging later in life. Further research will be needed to determine the potential of such effect modification in other populations. In addition, identifying the association between *APOE* and intellectual factors other than educational attainment during different periods of life and investigating how those factors

might modify the effect of *APOE* on late-life cognition will provide a more comprehensive picture of the effect of *APOE* on lifetime cognitive abilities.

Chapter 7
Overall Discussion

The overall purpose of this study was to identify the longitudinal patterns of cognitive state changes and the factors associated with those patterns in older adults. This purpose was addressed through the specific aims of three separate but interconnected studies (Chapters 4 to 6). The first study (Chapter 4) identified and compared patterns of cognitive state changes among older adults using two diverse methods. Predictors of these temporal patterns of cognitive state changes identified by the preferred method were then investigated in the second and third studies. The second study (Chapter 5) determined their association with academic achievement (educational attainment and academic performance). The third study (Chapter 6) investigated the association of *APOE*-ε4 with cognition both earlier and later in life, where earlier-life cognition was measured using educational attainment and later-life cognition was measured using patterns of cognitive state changes. Educational attainment was also examined as a potential modifier of the association between *APOE* status and patterns of cognitive state changes later in life.

In Chapter 4, using longitudinal data from the Nun Study, cognitive aging was modeled through trajectories of change across four cognitive states: normal cognition, mild cognitive impairment (MCI), global impairment (GI), and dementia. Individuals were grouped into distinct patterns of cognitive state changes using two methods: a clinically-driven approach and a statistical modeling approach, latent class mixed-effects modeling (lcmm). Using the clinically-driven approach, cognitive state changes were clustered into seven distinct patterns distinguishing between trajectories with and without cognitive improvement, and with and without progression to dementia. In contrast, the lcmm approach identified four latent classes of cognitive state changes from better cognitive function (Class 1) to worse (Class 4). The results from the clinically-driven approach were preferred for identifying distinct patterns of

cognitive state changes because of the ability of these patterns to capture more clinically meaningful details compared to the latent classes identified using the lcmm approach.

The types of cognitive state changes observed in Chapter 4 are consistent with those previously reported. Evidence of reverse transition from cognitive impairment to normal cognition has been noted within the Nun Study as well as other populations (Abner et al., 2012; Iraniparast et al., 2016; Koepsell & Monsell, 2012; Malek-Ahmadi, 2016). Categories of cognitive decline observed using our two analytic methods were also reported in previous studies of transitions from normal cognition to MCI and from MCI to dementia using multi-state Markov modeling (Kryscio et al., 2008; Riley et al., 2000; Tyas et al., 2007). In addition, the patterns of cognitive state changes that were identified using the clinically-driven approach expand patterns that were reported previously by Aiken-Morgan et al. (2017). While broadly consistent with these findings, Chapter 4 expands previous studies on cognitive aging to model the broad definition of cognitive states through temporal patterns of cognitive state changes including decline and improvement each with or without progression to dementia.

In Chapter 5, higher academic achievement, as evidenced by educational attainment or performance in high school courses, was associated with cognitive reserve through experiencing healthier patterns of cognitive state changes than the reference pattern of stable dementia. The results suggest that academic achievement can contribute to cognitive reserve through four categories of evidence: 1) better cognitive performance upon reaching older age; 2) slower rate of cognitive decline; 3) delayed onset of dementia or delayed accelerated decline; and 4) reversion from a more to less impaired cognitive state. First, results reflecting a higher cognitive level upon reaching older age among more highly educated participants are consistent with previous research that found higher educational attainment was associated with better cognitive performance upon reaching adulthood or older age (Alley et al., 2007; McDermott et al., 2016; Mungas et al., 2018; Y. Stern et al., 2018; Tucker-Drob et al., 2009; Wilson et al., 2019; Zahodne et al., 2015). Second, results showing that higher academic

achievement was associated with patterns of cognitive state changes consistent with a slower cognitive decline is congruous with reports of an effect of higher education on slower rates of decline (Alley et al., 2007; McDermott et al., 2016; Reas et al., 2017; Zahodne et al., 2015). Third, in our study, higher academic achievement increased the odds of experiencing trajectories of cognitive decline without dementia. For those individuals who did progress to dementia, higher educational attainment increased the odds of experiencing a pattern of fewer years with dementia. Both results provide evidence of a delayed onset of dementia. Similar effects of delay in progressive cognitive decline have previously been observed through delayed accelerated decline (Clouston et al., 2019; Hall et al., 2007; Y. Stern et al., 2018). Fourth, higher educational attainment distinguished membership in a pattern of cognitive decline and improvement from a pattern of stable dementia. This supports previous research that higher educational attainment builds cognitive reserve that may lead to reverse transition from MCI to normal cognition (Canevelli et al., 2016; Sachdev et al., 2013; Xue et al., 2019).

The third study (Chapter 6) used the same longitudinal data as the studies in Chapters 4 and 5. The results from Chapter 6 did not support the first part of the antagonistic pleiotropy hypothesis for *APOE:* that *APOE*-ε4 is associated with higher cognitive abilities earlier in life (in this study measured by educational attainment). However, results did support the second part of the hypothesis, finding that *APOE*-ε4 was associated with lower cognitive performance later in life. *APOE*-ε4 carriers had lower odds than non-carriers of experiencing healthier patterns of cognitive state changes than the least healthy pattern (stable dementia). The third part of the hypothesis was also supported because higher educational attainment (a graduate degree) was observed to compensate for the detrimental effect of *APOE*-ε4 on cognition later in life. Overall, as this study did not support the first part of the antagonistic pleiotropy hypothesis for *APOE*, it did not provide support that *APOE* has an antagonistic pleiotropy effect on cognition. Matching this part of the results from Chapter 6 to the cognitive reserve results observed in Chapter 5, cognitive reserve was observed to

compensate for the detrimental effects of *APOE*-ε4 and older age on cognition later in life, and the level of reserve increased with higher levels of education.

The lack of a significant association between *APOE*-ε4 and higher educational attainment earlier in life observed in Chapter 6 is consistent with a number of studies that have also not found such beneficial effects for *APOE*-ε4 carriers (Bretsky et al., 2003; Hiekkanen et al., 2009; F. Liu et al., 2010; O'Donoghue et al., 2018), although research supporting a beneficial effect of *APOE*-ε4 on early-life cognition has also been frequently reported (Tuminello & Han, 2011). In addition, controversy exists on the neurobiological mechanism for an association between *APOE* and cognition in early life. A wide range of neuroimaging research has found that, during a memory task, *APOE*-ε4 carriers have higher brain activity than non-carriers (Filbey et al., 2006; Filbey et al., 2010; Filippini et al., 2009), which is sometimes considered as a sign of a beneficial effect of *APOE*-ε4 on early-life cognition (Mondadori et al., 2006). However, other research (Tuminello & Han, 2011) including a recent study by Hodgetts et al. (2019), has suggested that this higher brain activity in younger *APOE*-ε4 carriers may be a result of "lifespan systems vulnerability" that increases activity in areas of brain that were affected by early neuropathological signs of Alzheimer's disease (Buckner et al., 2009; de Haan et al., 2012; Jagust & Mormino, 2011).

The significant association between *APOE*-ε4 and experiencing the pattern of stable dementia versus healthier patterns of cognitive state changes later in life that was observed in Chapter 6 is also consistent with the results of biological and epidemiological studies that found an increased risk of Alzheimer's pathology and dementia among *APOE*-ε4 carriers (Chuang et al., 2010; Dickson et al., 2018; Glorioso et al., 2019; Llewellyn et al., 2010; Schmechel et al., 1993). Previous research in the Nun Study also showed that *APOE*-ε4 was associated with the risk of cognitive impairment and dementia (Riley et al., 2000; Tyas et al., 2007). Finally, the reduced detrimental effect of *APOE*-ε4 on late-life cognition among individuals with higher educational attainment observed in this study is also consistent with

previous reports for other types of cognitive outcomes (Arenaza-Urquijo et al., 2015; Reas et al., 2019; Tyas et al., 2007).

This dissertation has several strengths in its examination of the longitudinal patterns of cognitive state changes and their predictors in older adults, including characteristics of the underlying data from the Nun Study as well as the analytic approaches. The Nun Study is a longitudinal study with annual cognitive assessments over 15 years of follow-up with available data on two measures of academic achievement earlier in life and on *APOE*, the most significant genetic risk factor for dementia. This rich data set allowed: 1) identification of distinct temporal patterns of cognitive state changes; 2) investigation into how academic achievement may contribute to cognitive reserve; and 3) examination of the effect of *APOE* on both early and late-life cognition in the same analytic sample to test the antagonistic pleiotropy hypothesis. In addition, the Nun Study provides a robust data set for studying cognitive aging because few participants missed follow-up assessments. Assessments included specific cognitive domains and overall cognition as well as functional ability measured through activities of daily living. The homogeneity of the study participants controlled for many potential confounding factors. In addition, this community-based sample provided the opportunity to model natural cognitive trajectories. These trajectories are relevant particularly when interventions are not possible or feasible due to financial constraints or other health conditions, or when interventions do not help to modify progression.

Both analytical approaches that were used in Chapter 4 have specific strengths in identifying distinct patterns or classes of cognitive state changes in older adults. A strength of the clinically-driven approach is in providing patterns that are more likely to be clinically meaningful than the results of the statistical modeling lcmm approach. The clinically-driven approach that was used in Chapter 4 can be modified and applied to other studies of aging and cognition with ordinal cognitive state levels. A strength of the lcmm approach is in its ability to distinguish significantly different classes of cognitive trajectories (latent classes). In

addition, in contrast with the clinically-driven approach, the lcmm approach models the actual age at cognitive assessments rather than the order of assessments. Finally, both the clinically-driven and the lcmm approaches allow inclusion of participants who miss some follow-up assessments (Proust-Lima et al., 2017).

Comparing the results of the clinically-driven approach with the lcmm approach (Chapter 4) allowed for assessment of the performance of this statistical modeling approach in terms of its ability to identify clinically meaningful latent classes that could be applied more often in the future to longitudinal studies of aging and cognition. This comparison provided knowledge on the potential clinical aspects of cognitive trajectories that might be missed in the lcmm approach and potential factors that cannot easily be considered in a clinically-driven approach.

In addition, the bias reduction multinomial logistic regression models that were used in Chapters 5 and 6 to model the association between covariates and patterns of cognitive state changes allowed estimation of odds ratios and their corresponding confidence intervals for all levels of exposures and outcomes when regular multinomial logistic regression was unable to estimate these parameters. While application of these bias reduction models can be computationally very intensive, recent software developments (brglm2) package (I. Kosmidis et al., 2018) has made their application easier and efficient.

This dissertation also has limitations. While the goal of this work was not to predict patterns of cognitive state changes in other population of older adults, generalizability of the results is likely of interest. The Nun Study participants are a special population who are not representative of the general population of older women in a general population, so over-interpretation should be avoided. Also, while annual cognitive assessments were frequent enough to capture most details of cognitive trajectories, some transitions may have happened between assessments. Data collection for the Nun Study began after age 65 when cognitive impairment and dementia might have already begun; therefore, cognitive trajectories before data collection could not be studied. Furthermore, participants who remained alive at the end

of the data collection could not be observed for their full cognitive trajectories. Finally, treatment of factors that led to cognitive impairment could contribute to reverse transitions from MCI to normal cognition. However, data on such potential interventions were not available.

Limitations of the analytical approaches in Chapter 4 vary by the type of approach used to identify the distinct patterns of cognitive state changes. Applying the clinically-driven method to identify patterns of cognitive state changes was time-intensive. However, now that these patterns have been identified, this approach can be more easily applied to other populations. The lcmm approach identified meaningful classes of cognitive state changes; however, some clinically meaningful details of trajectories were not captured. Lack of a good fit of the lcmm model to the data set (i.e., not a good absolute fit) could explain why some clinically meaningful details of the cognitive state changes were not captured using the statistical modeling approach. The BIC and average posterior probabilities that were used to identify the best lcmm model were only able to check the relative fit of the models with different numbers of latent classes; a standardized method for checking the absolute fit of an lcmm model is not trivial and is not currently available. However, the goodness of fit of the lcmm models was checked by a geriatrician for face validity. In addition, using bias reduction multinomial logistic regression to estimate associations for categories with zero or few observations causes difficulties for interpretation when there are wide confidence intervals. In Chapters 5 and 6, the goodness of fit tests for all multinomial models was not rejected; however, statistically, the validity of these tests in the presence of sparse observations, needs to be checked in future research.

Further research is needed to determine patterns of cognitive trajectories in other populations and their predictors to target interventions of modifiable risk factors and promote healthy cognitive aging. Future research is also needed to examine how type and timing of interventions may influence cognitive trajectories. More studies are needed to test how different measures of cognitive development earlier in life may contribute to cognitive

reserve. Finally, this study on the potential antagonistic pleiotropy effect of *APOE* on cognition should be repeated in larger populations with more diverse levels of education.

Despite the limitations mentioned, this dissertation contributes to our understanding of healthy cognitive aging and its predictors. Overall, the trajectories of cognitive aging seen in this dissertation were heterogeneous and included substantial proportions of older adults in trajectories reflecting cognitive reserve. A possible explanation for this heterogeneity in patterns of cognitive state changes includes intellectual and genetic factors, such as those investigated in this dissertation. Higher academic achievement can contribute to building cognitive reserve through higher cognitive levels upon reaching older age, a slower rate of cognitive decline, reversion to a higher cognitive level after showing signs of impairment, and, when dementia does occur, a delay in its onset. Understanding the association between academic achievement and cognitive aging can contribute to developing strategies to develop cognitive reserve and promote healthy cognitive aging. In addition, understanding the association between *APOE* and earlier and later-life cognition may be useful for researchers targeting *APOE* to develop interventions that consider non-genetic factors that may modify the effect of *APOE* on cognition.

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Appendix A

Diagnosis for cognitive states in the Nun Study

Table A-1 Diagnostic criteria for cognitive states in the Nun Study

Criteria	Normal	Mild Cognitive Impairment		Global Impairment		Dementia	
Activities of Daily Living (ADL)	≥ 4	≥ 4		Impairment in ADL or MMSE		Impaired in ADL	
Global Cognition							
MMSE	≥ 24	≥ 24				Impaired (< 24)	
CERAD neuropsychological battery							
Delayed Word Recall	≥ 5	< 5	Impaired in at least one	< 5	Impaired in at least one	Impaired (< 4)	
Boston Naming	≥ 14	< 14		< 14		< 13	Impaired in at least one
Verbal Fluency	≥ 12	< 12		< 12		< 11	
Constructional Praxis	≥ 9	< 9		< 9		< 8	
Decline in function from a previous level						Present	

Abbreviations: ADL = Activities of daily living: feeding, dressing, walking, standing [transferring], and toileting; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; MMSE = Mini-Mental State Examination;

Appendix B

Tabular overview of similar and dissimilar cognitive trajectories in the Nun Study

Table B-1 Overview of similar cognitive trajectories in the Nun Study: decline and improvement without developing dementia

		Assessment Wave												Death
		1	2	3	4	5	6	7	8	9	10	11	12	
Participant	Age	81	82	84	86	87	88	90	91	92	93	94	95	95
1	Cognitive state[1]	3	4	4	3	4	4	4	4	4	3	4	4	N.A.
	Age	78	79	80	82	83	85	87	88	89	90	91	92	93
2	Cognitive state	4	3	3	3	4	4	3	4	4	2	3	2	N.A.
	Age	85	86	88	89	91								92
3	Cognitive state	3	4	4	3	3								N.A.
	Age	77	79	81	83	84	85	87	88	89	90	91	92	N.A.
4	Cognitive state	3	3	4	3	3	3	4	3	2	2	2	2	N.A.
	Age	79	81	82	84	85	87	88	89	90	91	92	93	N.A.
5	Cognitive state	4	3	3	2	4	4	3	4	4	3	4	3	N.A.

[1]Cognitive state 4 = normal cognition, 3 = mild impairment, 2 = global impairment, 1 = dementia
Abbreviation: N.A = not applicable

Table B-2 Overview of similar cognitive trajectories in the Nun Study: progressive decline leading to dementia

		Assessment Wave												Death
		1	2	3	4	5	6	7	8	9	10	11	12	
#	Age	77	79	80	82	83	84	86	87	88	89	90	91	N.A.
1	Cognitive state[1]	4	4	4	4	4	2	2	2	1	1	1	1	N.A.
	Age	76	78	80	82									83
2	Cognitive state	2	1	1	1									N.A.
	Age	83	84	85	87									87
3	Cognitive state	3	3	1	1									N.A.
	Age	77	78	80	82	83	84	86						87
4	Cognitive state	2	1	1	1	1	1	1						N.A.
	Age	92	93	94	96	98	99	101						101
5	Cognitive state	3	2	2	1	1	1	1						N.A.

[1]Cognitive state 4 = normal cognition, 3 = mild impairment, 2 = global impairment, 1 = dementia
Abbreviation: N.A. = not applicable

Appendix C

Latent class mixed-effects modeling

Latent class analysis was first introduced by Lazarsfeld and Henry in 1968 to cluster individuals into homogeneous groups according to their cross-sectional measurement on variables of interest (Lazarsfeld & Henry, 1968). In this thesis, distinct patterns of cognitive state changes were identified based on semi-parametric modeling using latent class mixed-effects modeling (lcmm) for longitudinal outcomes (Proust-Lima et al., 2017), which are annual cognitive assessments. In lcmm, the term "latent classes" refers to those different clusters of individuals who share similar trajectories of cognitive state changes over time; "mixed modeling" refers to how both fixed and random effects explain the trajectories of cognitive state changes.

The participants of the Nun Study are assumed to have G heterogeneous patterns of cognitive state changes (latent classes). For each participant, i, in the sample of 574 individuals ($i = 1, 2, \dots, 574$), a vector of n_i repeated cognitive assessments is available that can be shown as $Y_i = (Y_{i1}, Y_{i2}, .., Y_{ij}, \dots, Y_{in_i})^T$, where Y_{ij} is the cognitive state for each individual i at assessment j that was performed at time t_{ij} and T represents the transposed matrix that is a new matrix whose rows are the columns of the original matrix. The underlying latent process for participant i, $\Lambda_i(\mathrm{t})$, is modeled based on

$$\Lambda_i(t)|_{c_i=g} = X_{L1i}(t)^T\beta + X_{L2i}(t)^T\alpha_g + Z_i(t_{ij})^T u_{ig} + \omega_i(t_{ij})$$

where c_i is the latent variable with up to G groups ($c_i = 1, 2, \dots, \mathrm{g}, \dots, G$). $X_{L1i}(t)$ is the vector of covariates with common population-level fixed effects, β ,over latent classes; $X_{L2i}(t)$ represents the vector of covariates with class-specific fixed effects, α_g; $Z_i(t_{ij})$ represents individual-specific random effects for subject i in each latent class, u_{ig}; and $\omega_i(t_{ij})$ accounts for uncertainty not described by the fixed effects and subject-specific random effects and is a zero mean Gaussian stochastic process (Proust-Lima et al., 2017).

Appendix D

Figure of trajectories of cognitive state changes for all participants within the same pattern identified using the clinically-driven approach (N = 574)

In the following figures, black trajectories represent participants who died before the end of the data collection period; orange trajectories represent participants who remained alive until the end of the data collection. Cognitive states are labelled from 1 to 4, with 4 = normal cognition, 3 = mild cognitive impairment, 2 = global impairment, and 1 = dementia.

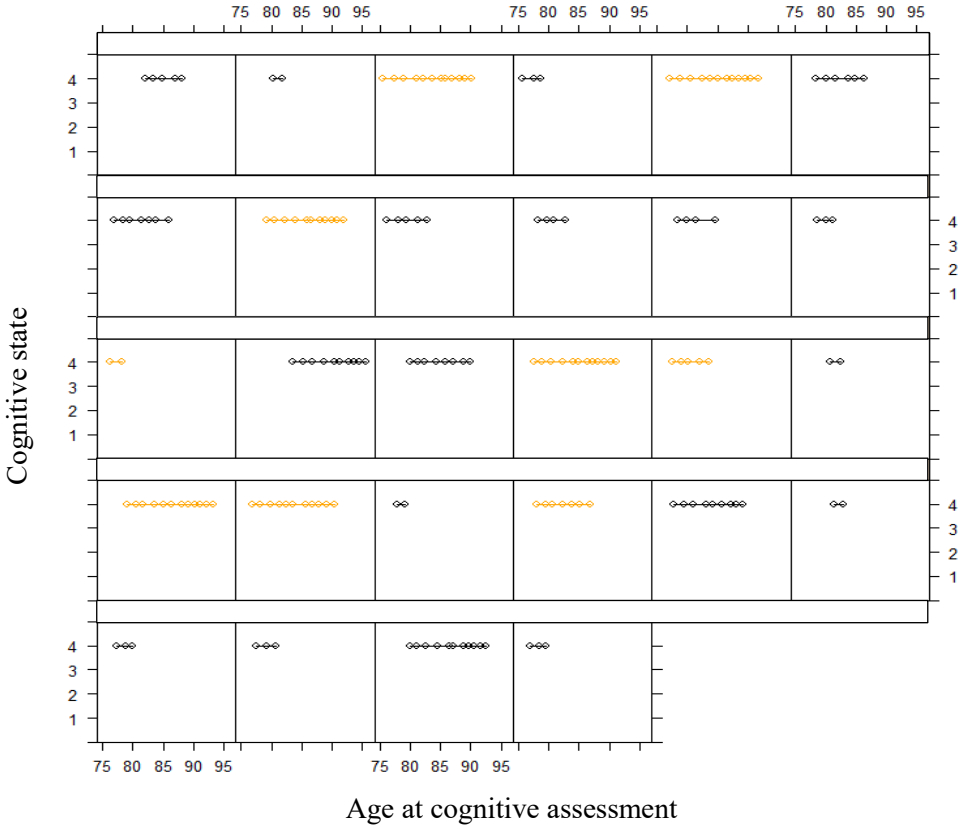

Figure D-1a First of seven clinically-driven patterns of cognitive state changes: stable normal cognitive state (N = 28)

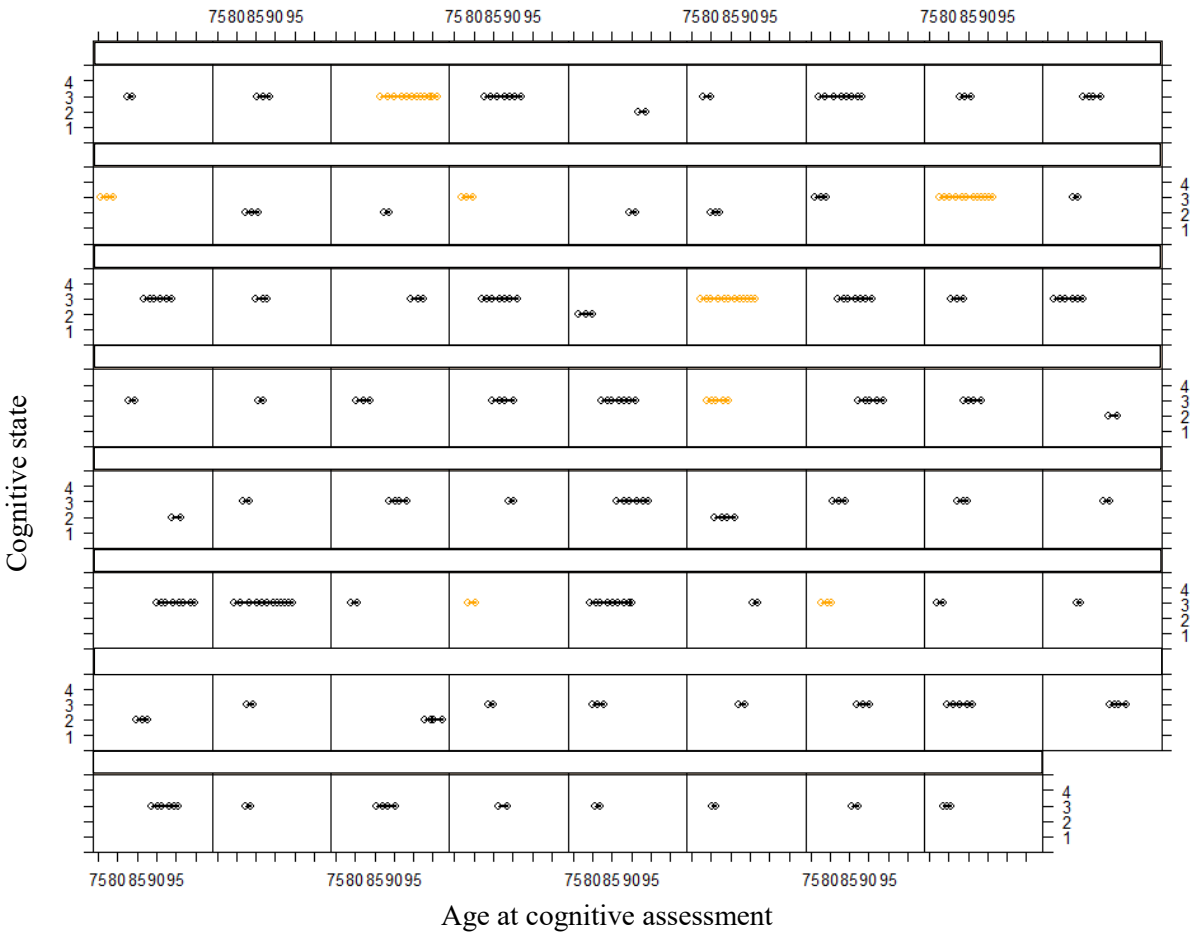

Figure D-1b Second of seven clinically-driven patterns of cognitive state changes: stable mild cognitive impairment or global impairment state (N = 71)

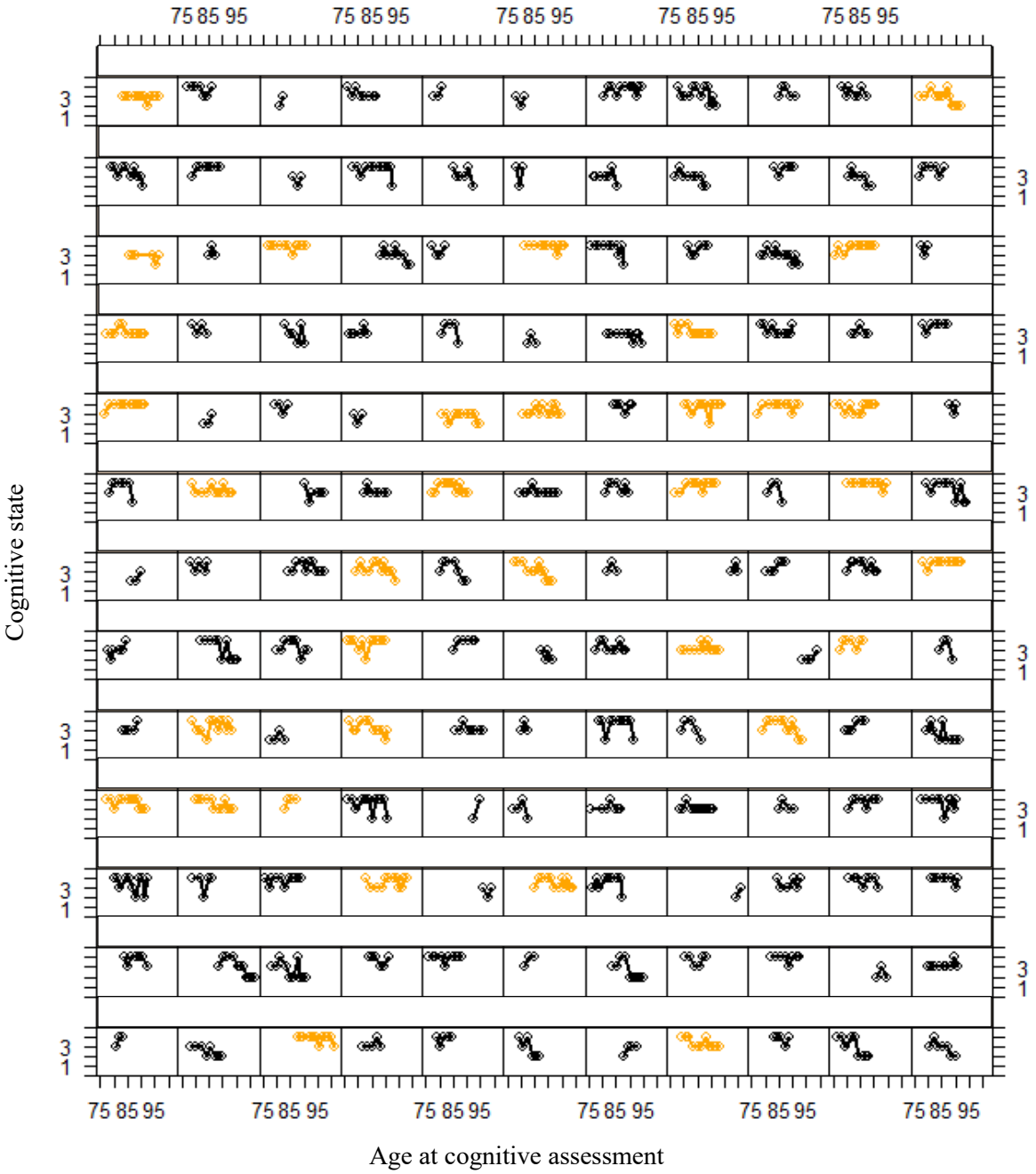

Figure D-1c Third of seven clinically-driven patterns of cognitive state changes: trajectories with decline and improvement without developing dementia (N = 143)

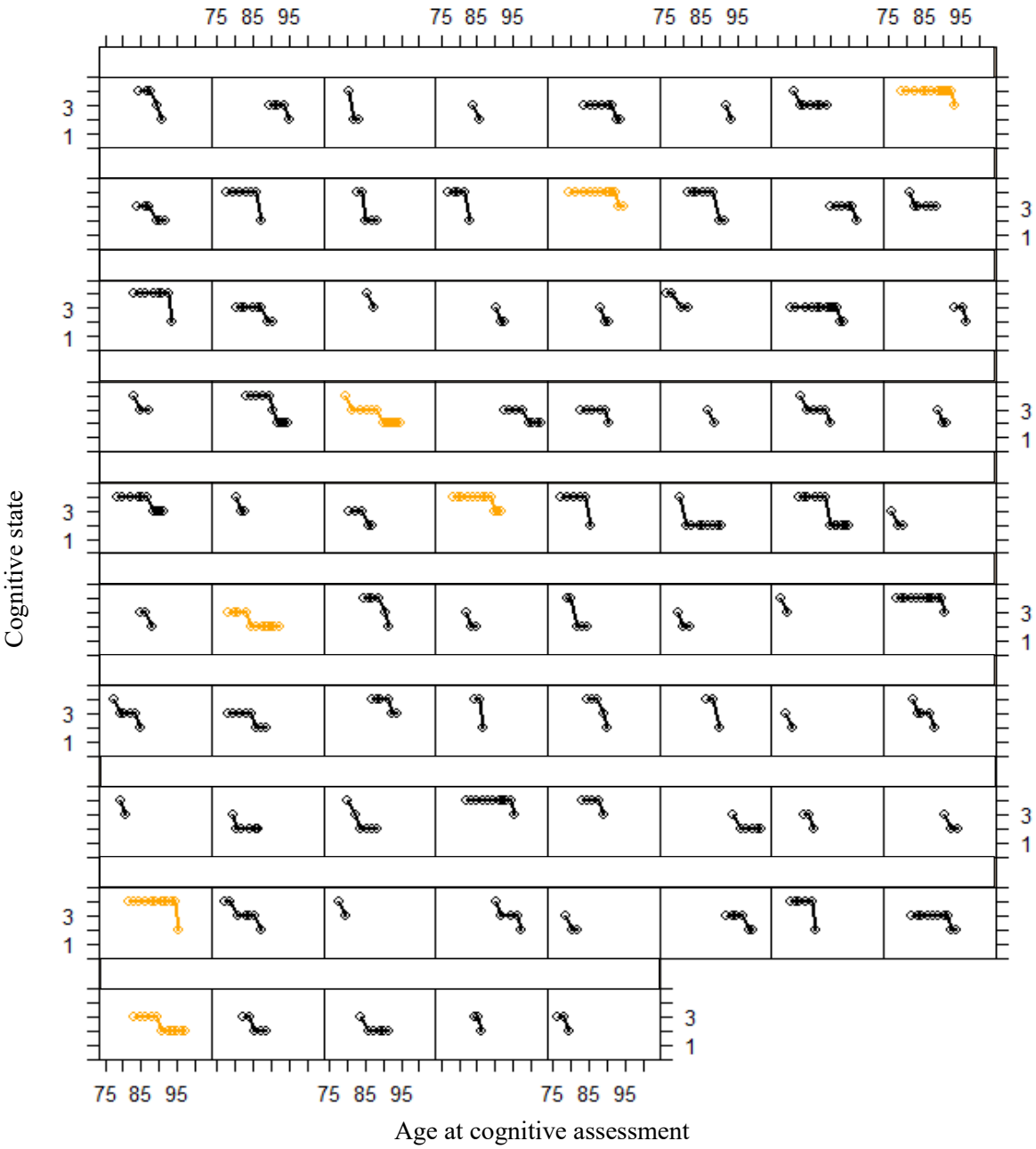

Figure D-1d Fourth of seven clinically-driven patterns of cognitive state changes: trajectories with progressive decline without development of dementia (N = 77)

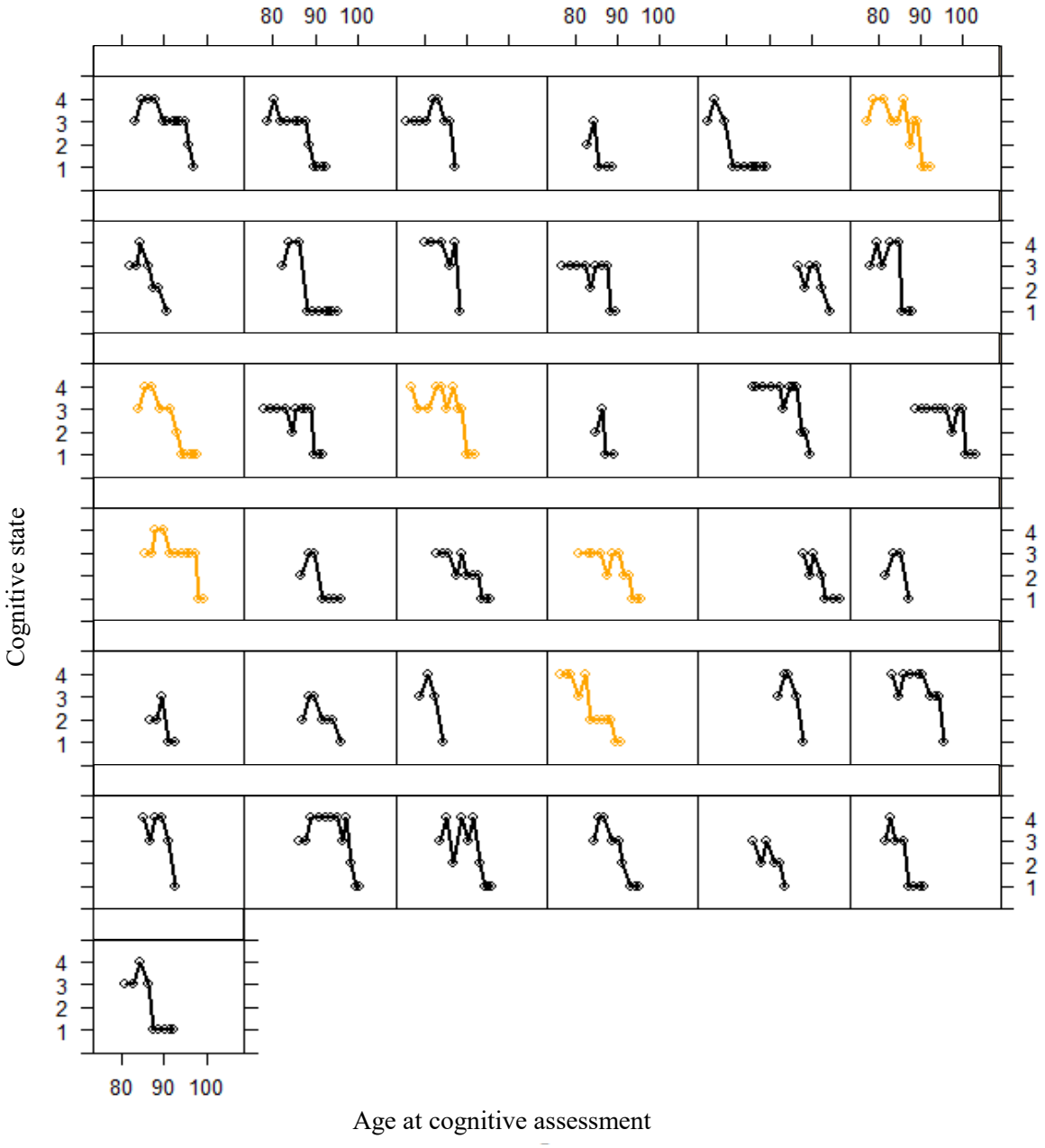

Figure D-1e Fifth of seven clinically-driven patterns of cognitive state changes: trajectories with decline and improvement with development of dementia (N = 37)

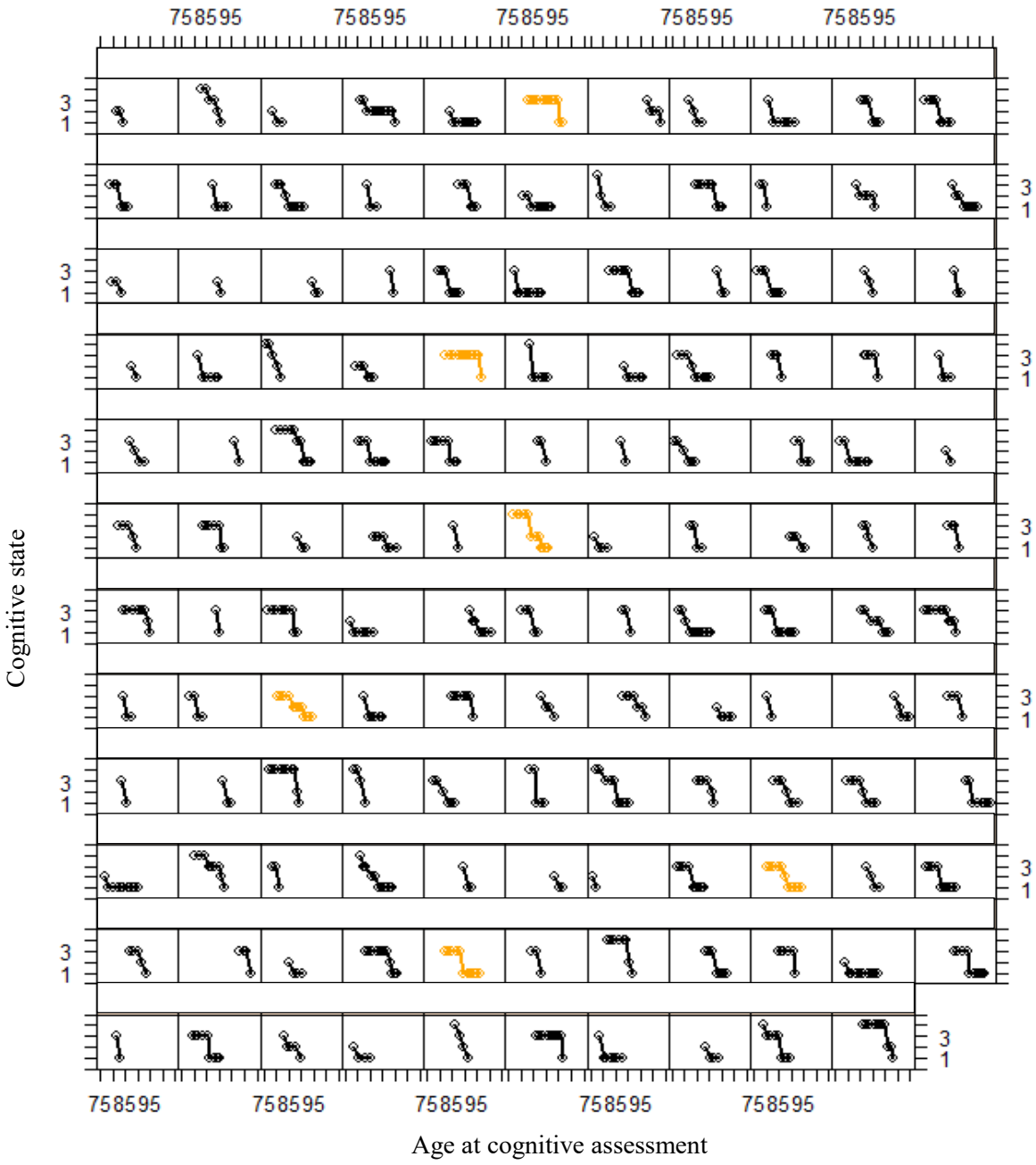

Figure D-1f Sixth of seven clinically-driven patterns of cognitive state changes: trajectories with progressive decline without development of dementia (N = 131)

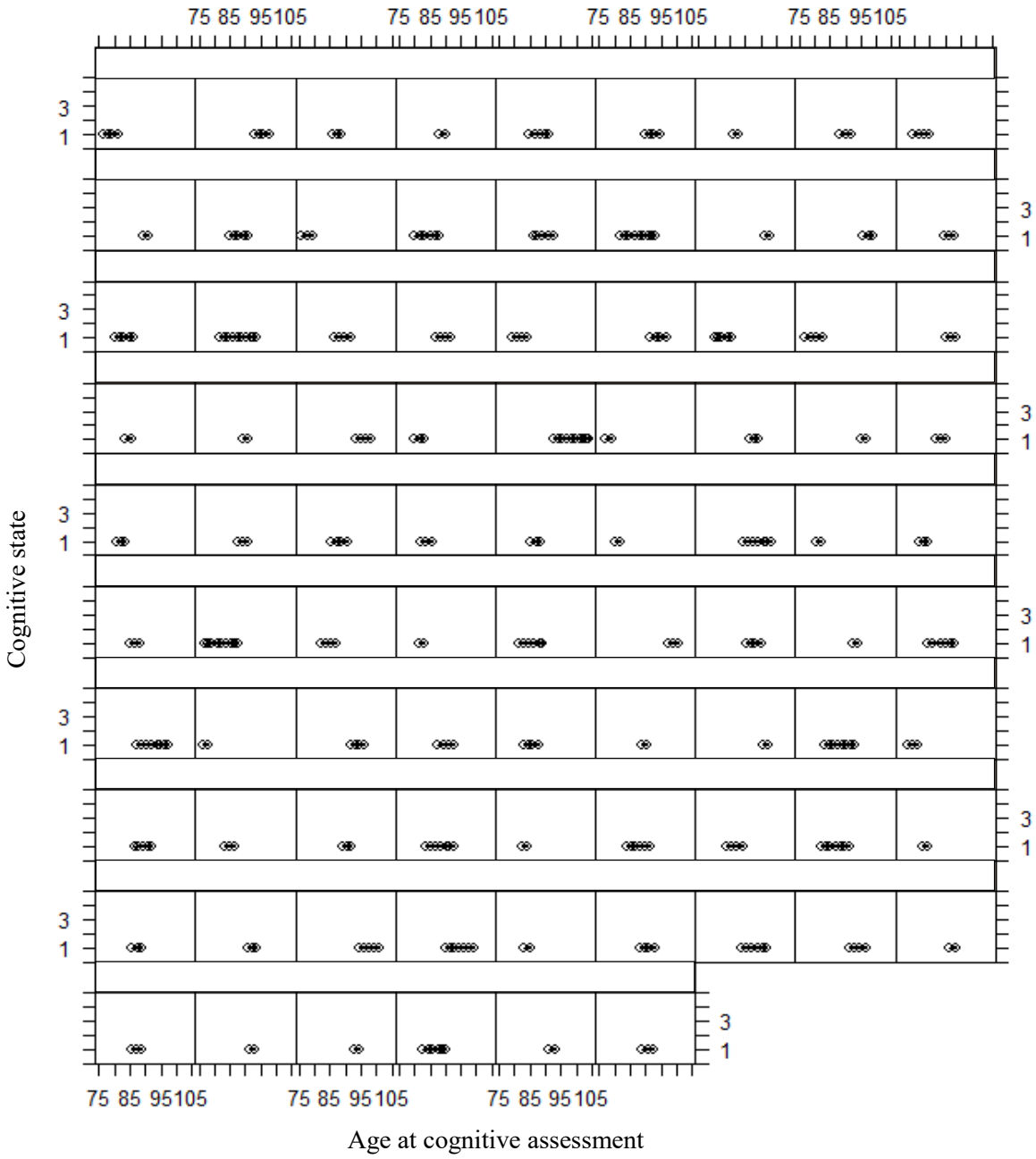

Figure D-1g Seventh of seven clinically-driven patterns of cognitive state changes: stable dementia cognitive state (N = 87)

Figure D-1 Patterns of cognitive state changes based on the clinically-driven approach (N = 574)

Appendix E

Figure of trajectories of cognitive state changes for all participants within the same latent classes identified using the latent class mixed-effects modeling (lcmm) approach (N = 574)

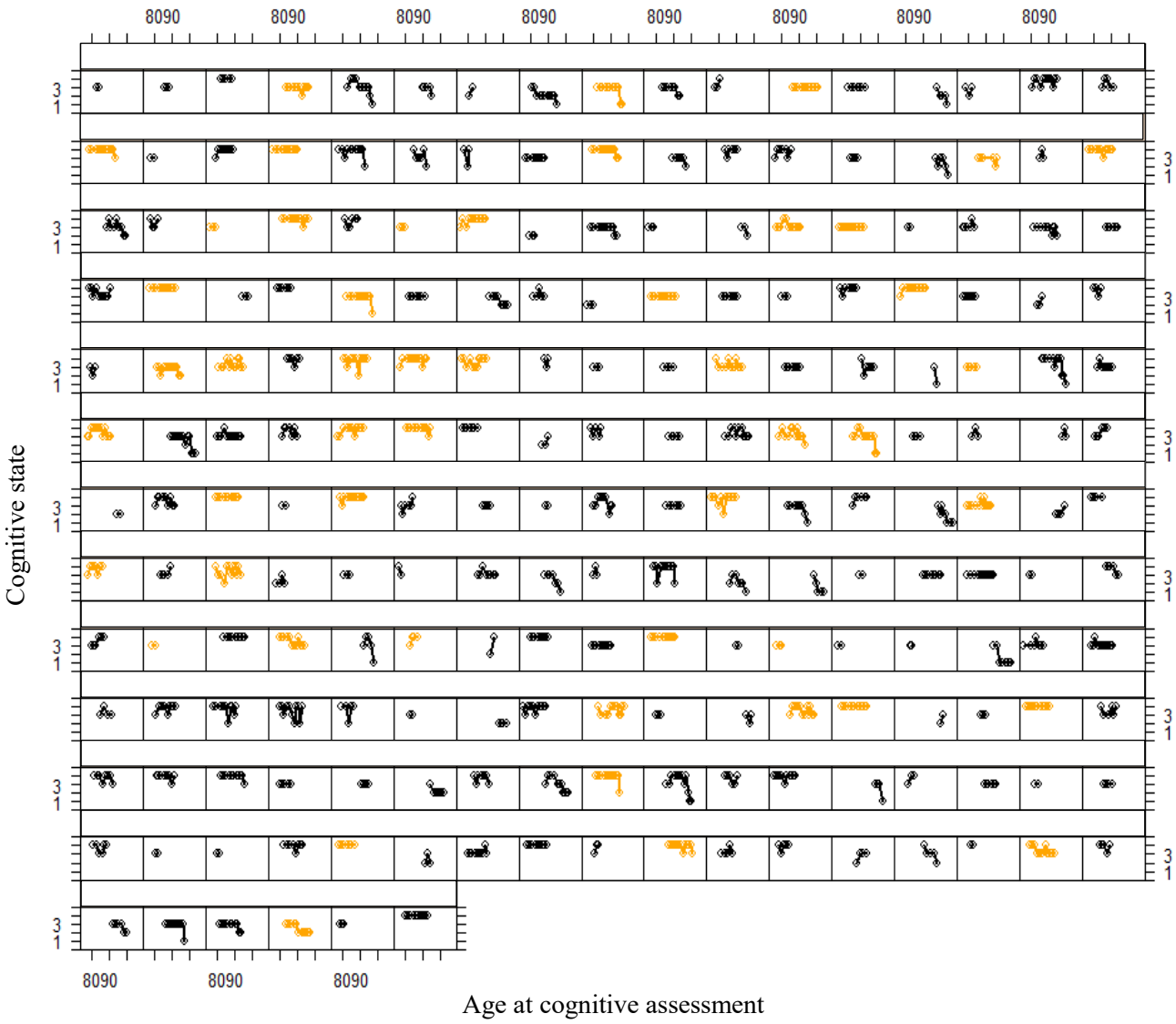

Figure E-1a First of four classes of cognitive state changes based on lcmm (N = 210)

Figure E-1b Second of four classes of cognitive state changes based on lcmm (N = 191)

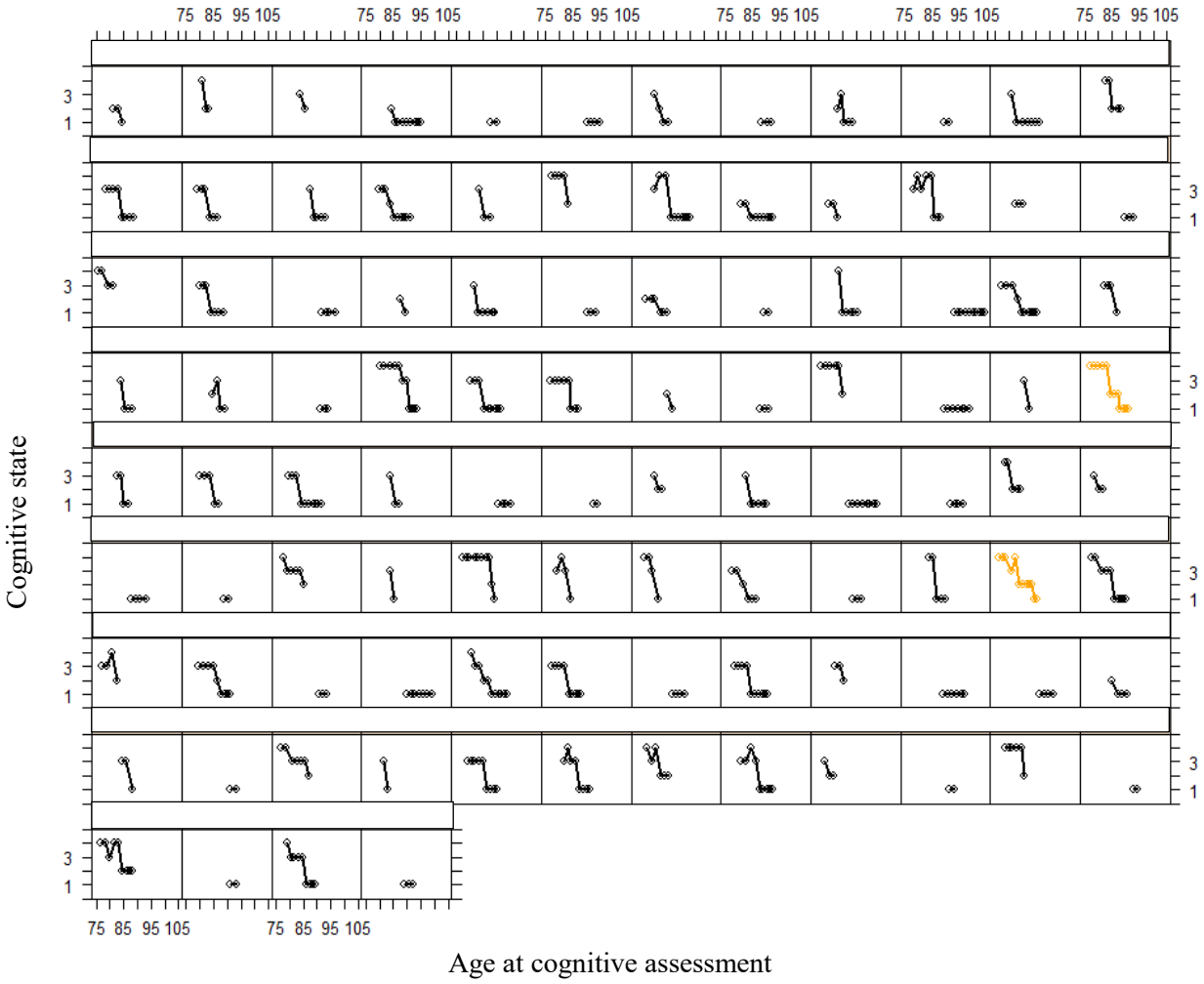

Figure E-1c Third of four classes of cognitive state changes based on lcmm (N = 100)

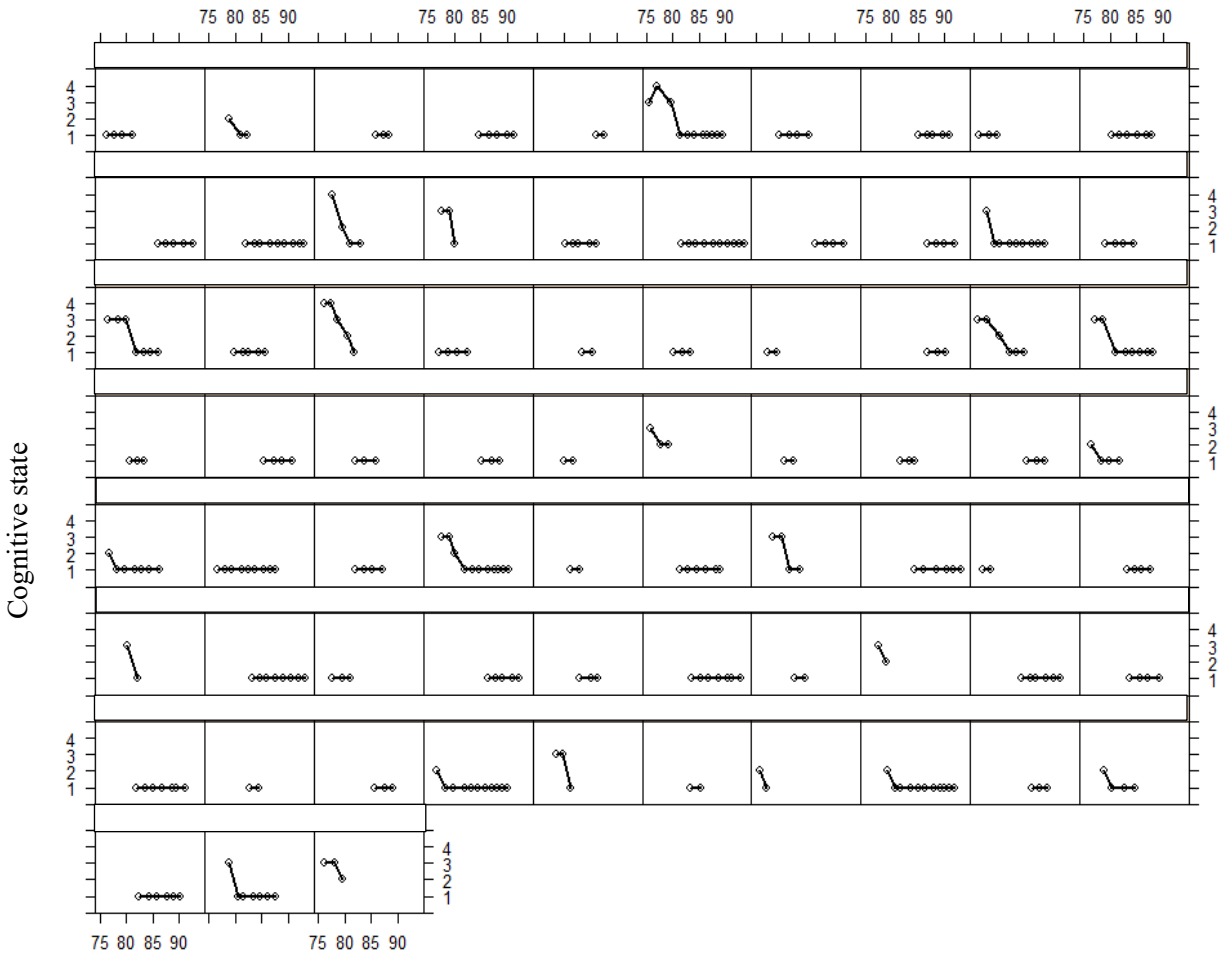

Figure E-1d Fourth of four latent classes of cognitive state changes based on lcmm (N = 73)

Figure E-1 Classes of cognitive state changes based on the latent class mixed-effects modeling approach with random intercept, age, and age squared (N = 574)

Black trajectories represent participants who died before the end of the data collection period; orange trajectories represent participants who remained alive until the end of the data collection. Cognitive states: 4 = normal cognition, 3 = mild cognitive impairment, 2 = global impairment, and 1 = dementia

Appendix F Characteristics of participants within patterns of cognitive state changes

Table F-1 Characteristics of participants within patterns of cognitive state changes (N = 411)

	Patterns[1] of cognitive state changes							
Characteristics	1	2	3	4	5	6	7	Total
Mean age, years (SD)								
Age at first assessment	78.32 (1.91)	83.16 (4.73)	80.97 (4.32)	81.99 (4.36)	82.91 (5.68)	83.55 (5.16)	86.13 (5.40)***	82.64 (5.09)
Age at last assessment	86.58 (5.08)	87.87 (5.43)	90.37 (4.32)	89.38 (5.31)	93.88 (5.31)	90.86 (4.81)	90.35 (5.44)***	90.22 (5.15)
Age at death	87.35 (4.71)	88.98 (5.27)	90.55 (4.32)	90.00 (5.18)	94.27 (5.72)	91.48 (4.77)	91.23 (5.57)***	90.82 (5.11)
Years of follow-up, mean (SD)	8.26 (4.36)	4.71 (3.60)	9.40 (4.05)	7.39 (3.98)	10.96 (3.22)	7.32 (3.63)	4.22 (2.61)***	7.58 (4.18)
Years between last assessment and death, mean (SD)	2.11 (3.17)	1.33 (1.63)	0.92 (1.03)	1.04 (1.49)	0.56 (0.39)	0.69 (0.51)	0.88 (1.29)**	0.92 (1.25)
APOE-ε4 allele, n (%)								
Present	2 (10.53)	7 (20.00)	11 (9.82)	14 (23.73)	5 (16.13)	31 (30.69)	19 (35.19)	89 (21.65)
Absent	17 (89.47)	28 (80.00)	101 (90.18)	45 (76.27)	26 (83.87)	70 (69.31)	35 (64.81)**	322 (78.35)
Education, n (%)								
≤ High school	0 (0.00)	1 (2.86)	4 (3.57)	1 (1.69)	2 (6.45)	7 (6.93)	9 (16.67)	24 (5.84)
Bachelor's degree	3 (15.79)	18 (51.43)	45 (40.18)	29 (49.15)	14 (45.16)	50 (49.50)	32 (59.26)	191 (46.47)
≥ Master's degree	16 (84.21)	16 (45.71)	63 (56.25)	289 (49.15)	15 (48.39)	44 (43.56)	13 (24.07)*	196 (47.69)
Academic performance								
GPA, mean (SD)	86.35 (6.75)	88.25 (5.70)	86.97 (6.63)	88.38 (5.46)	86.18 (5.62)	86.14 (6.37)	85.88 (6.35)	86.85 (6.25)
Total sample	19	35	112	59	31	101	54	411
Death frequency, n (%)	13 (68.42)	33 (94.29)	87 (77.68)	54 (91.53)	25 (80.65)	98 (97.03)	54 (100)	364 (88.56)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; GPA = grade point average; SD = standard deviation

*p < 0.05; **p < 0.01; ***p < 0.001

Table F-2 Characteristics of participants within patterns of cognitive state changes (English subsample, N = 401)

	Patterns[1] of cognitive state changes							
Characteristics	1	2	3	4	5	6	7	Total
Mean age, years (SD)								
Age at first assessment	78.50 (1.92)	83.16 (4.73)	80.97 (4.34)	82.18 (4.32)	82.79 (5.73)	83.54 (5.19)	86.10 (5.44)***	82.69 (5.10)
Age at last assessment	87.19 (5.00)	87.87 (5.43)	90.34 (4.35)	89.62 (5.21)	93.81 (5.39)	90.90 (4.82)	90.34 (5.49)***	90.29 (5.12)
Age at death	87.64 (4.52)	88.98 (5.27)	90.51 (4.36)	90.26 (5.09)	94.16 (5.81)	91.51 (4.78)	91.21 (5.62)**	90.87 (5.10)
Years of follow-up, mean (SD)	8.69 (4.36)	4.71 (3.60)	9.37 (4.07)	7.44 (4.01)	11.02 (3.26)	7.36 (3.63)	4.24 (2.63)***	7.60 (4.19)
Years between last assessment and death, mean (SD)	1.70 (2.81)	1.33 (1.63)	0.95 (1.04)	1.05 (1.52)	0.55 (0.39)	0.68 (0.50)	0.86 (1.30)*	0.91 (1.20)
APOE-ε4 allele, n (%)								
Present	2 (11.76)	7 (20.00)	11 (10.09)	13 (22.81)	5 (16.67)	30 (30)	18 (33.96)	86 (21.45)
Absent	15 (88.24)	28 (80.00)	98 (89.91)	44 (77.19)	25 (83.33)	70 (7)	35 (66.04)**	315 (78.55)
Education, n (%)								
≤ High school	0 (0.00)	1 (2.86)	4 (3.67)	1 (1.75)	2 (6.67)	7 (7.00)	9 (16.98)	24 (5.99)
Bachelor's degree	3 (17.65)	18 (51.43)	44 (40.37)	28 (49.12)	13 (43.33)	50 (50.00)	31 (58.49)	187 (46.63)
≥ Master's degree	14 (82.35)	16 (45.71)	61 (55.96)	28 (49.12)	15 (50.00)	43 (43.00)	13 (24.53)*	190 (47.38)
Academic performance in English, mean (SD)	86.35 (8.42)	86.40 (6.76)	86.52 (7.66)	87.74 (7.10)	85.67 (8.29)	85.13 (7.20)	85.34 (7.91)	86.11 (7.51)
Total sample	17	35	109	57	30	100	53	401
Death frequency, n (%)	11 (64.71)	33 (94.29)	84 (77.06)	52 (91.23)	24 (80)	97 (97)	53 (100)	354

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; GPA = grade point average; SD = standard deviation

*p < 0.05; **p < 0.01; ***p < 0.001

Table F-3 Characteristics of participants within patterns of cognitive state changes (Latin subsample, N = 368)

Characteristics	Patterns[1] of cognitive state changes 1	2	3	4	5	6	7	Total
Age (years), mean (SD)								
Age at first assessment	78.33 (1.96)	83.19 (4.79)	81.06 (4.39)	81.68 (3.87)	82.70 (5.90)	83.50 (5.00)	86.36 (5.14)***	82.59 (5.00)
Age at last assessment	86.57 (5.22)	87.77 (5.49)	90.41 (4.47)	89.32 (4.90)	93.69 (5.40)	90.92 (4.69)	90.76 (5.03)***	90.23 (5.07)
Age at death	87.35 (4.71)	88.90 (5.34)	90.57 (4.47)	89.87 (4.73)	94.00 (5.87)	91.54 (4.65)	91.68 (5.16)**	90.81 (5.01)
Years of follow-up, mean (SD)	8.24 (4.49)	4.59 (3.58)	9.35 (4.13)	7.63 (3.96)	10.99 (3.28)	7.43 (3.68)	4.39 (2.72)***	7.64 (4.21)
Years between last assessment and death, mean (SD)	2.11 (3.17)	1.36 (1.65)	0.97 (1.08)	1.01 (1.54)	0.56 (0.40)	0.69 (0.50)	0.92 (1.37)**	0.95 (1.31)
APOE-ε4 allele, n (%)								
Present	2 (11.11)	7 (20.59)	11 (11.00)	14 (25.45)	5 (17.86)	28 (32.56)	15 (31.91)	82 (22.28)
Absent	16 (88.89)	27 (79.41)	89 (89.00)	41 (74.55)	23 (82.14)	58 (67.44)	32 (68.09)**	286 (77.72)
Education, n (%)								
≤ High school	0 (0)	1 (2.94)	4 (4.00)	1 (1.82)	2 (7.14)	4 (4.65)	6 (12.77)	18 (4.89)
Bachelor's degree	2 (11.11)	17 (50.00)	39 (39)	26 (47.27)	12 (42.86)	45 (52.33)	29 (61.70)	170 (46.20)
≥ Master's degree	16 (88.89)	16 (47.06)	57 (57)	28 (50.91)	14 (50.00)	37 (43.02)	12 (25.53)*	180 (48.91)
Academic performance								
Latin, mean (SD)	87.44 (6.55)	88.00 (8.37)	87.86 (7.90)	89.09 (7.11)	85.93 (8.65)	86.51 (7.79)	87.5531915	87.54 (7.79)
Total sample	18	34	100	55	28	86	47	368
Death frequency, n (%)	13 (72.22)	32 (94.12)	77 (77.00)	50 (90.91)	22 (78.57)	84 (97.67)	47 (100.00)	325

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; GPA = grade point average; SD = standard deviation

*p < 0.05; **p < 0.01; ***p < 0.001

Table F-4 Characteristics of participants within patterns of cognitive state changes (algebra subsample, N = 400)

Characteristics	Patterns[1] of cognitive state changes 1	2	3	4	5	6	7	Total
Age (years), mean (SD)								
Age at first assessment	78.37 (1.95)	83.16 (4.73)	81.04 (4.39)	82.07 (4.36)	82.91 (5.68)	83.61 (5.18)	86.19 (5.43)***	82.72 (5.12)
Age at last assessment	86.95 (4.95)	87.87 (5.43)	90.35 (4.40)	89.47 (5.21)	93.88 (5.31)	90.90 (4.85)	90.45 (5.44)***	90.28 (5.15)
Age at death	87.92 (4.42)	88.98 (5.27)	90.50 (4.42)	90.11 (5.10)	94.27 (5.72)	91.51 (4.81)	91.32 (5.58)***	90.88 (5.12)
Years of follow-up, mean (SD)	8.58 (4.25)	4.71 (3.60)	9.31 (4.10)	7.41 (4.00)	10.96 (3.22)	7.29 (3.66)	4.26 (2.62)***	7.56 (4.18)
Years between last assessment and death, mean (SD)	2.24 (3.27)	1.33 (1.63)	0.95 (0.06)	1.06 (1.52)	0.56 (0.39)	0.68 (0.51)	0.87 (1.30)***	0.93 (1.26)
APOE-ε4 allele, n (%)								
Present	2 (11.11)	7 (20)	11 (10.28)	13 (22.81)	5 (16.13)	30 (30.30)	19 (35.85)	87 (21.75)
Absent	16 (88.89)	28 (80)	96 (89.72)	44 (77.19)	26 (83.87)	69 (69.70)	34 (64.15)**	313 (78.25)
Education, n (%)								
≤ High school	0 (0)	1 (2.86)	4 (3.74)	1 (1.75)	2 (6.45)	6 (6.06)	9 (16.98)	23 (5.75)
Bachelor's degree	3 (16.67)	18 (51.43)	43 (40.19)	27 (47.37)	14 (45.16)	50 (50.51)	32 (60.38)	187 (46.75)
≥ Master's degree	15 (83.33)	16 (45.17)	60 (56.07)	29 (50.88)	15 (48.39)	43 (43.43)	12 (22.64)*	190 (47.50)
Academic performance								
Algebra, mean	85.72 (8.14)	89.43 (7.47)	87.12 (8.31)	88.91 (7.24)	87.61 (7.34)	86.69 (8.61)	85.58 (8.92)	87.24 (8.20)
Total sample	18	35	107	57	31	99	53	400
Death frequency, n (%)	12 (66.67)	33 (94.29)	82 (76.64)	52 (91.23)	25 (80.65)	96 (96.97)	53 (100)	353 (88.25)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; GPA = grade point average; SD = standard deviation

*p < 0.05; **p < 0.01; ***p < 0.001

Table F-5 Characteristics of participants within patterns of cognitive state changes (geometry subsample, N = 385)

Characteristics	Patterns[1] of cognitive state changes 1	2	3	4	5	6	7	Total
Age (years), mean (SD)								
Age at first assessment	78.37 (1.95)	82.84 (4.40)	81.00 (4.35)	82.08 (4.40)	82.43 (5.50)	83.58 (5.24)	86.20 (5.30)***	82.59 (5.05)
Age at last assessment	86.95 (4.95)	87.63 (5.32)	90.39 (4.43)	89.58 (5.24)	93.47 (5.25)	90.87 (4.95)	90.35 (5.61)***	90.19 (5.16)
Age at death	87.92 (4.42)	88.74 (5.17)	90.55 (4.43)	90.21 (5.13)	93.70 (5.67)	91.47 (4.89)	91.06 (5.52)**	90.75 (5.07)
Years of follow-up, mean (SD)	8.58 (4.25)	4.79 (3.63)	9.40 (4.06)	7.50 (3.98)	11.04 (3.24)	7.29 (3.60)	4.16 (2.51)***	7.61 (4.17)
Years between last assessment and death, mean (SD)	2.24 (3.27)	1.35 (1.65)	0.93 (1.06)	1.05 (1.52)	0.55 (0.41)	0.67 (0.48)	0.71 (0.52)***	0.91 (1.20)
APOE-ε4 allele, n (%)								
Present	2 (11.11)	7 (20.59)	10 (9.43)	14 (24.56)	5 (18.52)	28 (29.79)	17 (34.69)	83 (21.56)
Absent	16 (88.89)	27 (79.41)	96 (90.57)	43 (75.44)	22 (81.48)	66 (70.21)	32 (65.31)**	302 (78.44)
Education, n (%)								
≤ High school	0 (0.00)	1 (2.94)	4 (3.77)	1 (1.75)	2 (7.41)	6 (6.38)	8 (16.33)	22 (5.71)
Bachelor's degree	3 (16.67)	17 (50.00)	40 (37.74)	27 (47.37)	10 (37.04)	47 (50.00)	29 (59.18)	173 (44.94)
≥ Master's degree	15 (83.33)	16 (47.06)	62 (58.49)	29 (50.88)	15 (55.65)	41 (43.62)	12 (24.49)*	190 (49.35)
Academic performance								
Geometry, mean	86.78 (8.22)	88.91 (8.17)	86.98 (8.12)	88.32 (7.60)	86.85 (7.93)	86.89 (7.96)	86.06 (7.97)	87.19 (7.96)
Total sample	18	34	106	57	27	94	49	385
Death frequency, n (%)	12 (66.67)	32 (94.12)	82 (77.36)	52 (91.23)	21 (77.78)	92 (97.87)	49 (100)	340 (88.31)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; GPA = grade point average; SD = standard deviation

*p < 0.05; **p < 0.01; ***p < 0.001

Appendix G

The association of educational attainment with patterns of cognitive state changes

Table G-1 The association of educational attainment with membership in patterns of cognitive state changes (English subsample, N = 401)

	Pattern[1] 1 vs 7	**Pattern 2 vs 7**	**Pattern 3 vs 7**	**Pattern 4 vs 7**	**Pattern 5 vs 7**	**Pattern 6 vs 7**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Unadjusted						
Education (vs. ≤ high school)						
Bachelor's degree	2.11 (0.08–54.00)	3.27 (0.54–25.68)	2.98 (0.82–10.79)	5.73 (0.85–38.81)	1.63 (0.32–8.26)	2.03 (0.66–6.22)
≥ Master's degree	20.41 (0.89–469.02)	**7.74 (1.07–56.13)**	**9.62 (2.52–36.72)**	**13.37 (1.89–94.52)**	4.36 (0.83–23.02)	**4.08(1.23–13.49)**
Adjusted for age and *APOE*						
Education (vs. ≤ high school)						
Bachelor's degree	2.97 (0.10–89.33)	3.74 (0.54–26.00)	3.19 (0.78–13.06)	5.65 (0.80–39.65)	1.66 (0.32–8.60)	1.96 (0.62–6.16)
≥ Master's degree	16.91 (0.62–461.03)	6.74 (0.90–50.35)	**7.55 (1.73–32.89)**	**10.43 (1.41–77.47)**	3.76 (0.68–20.87)	3.43 (0.99–11.92)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; OR = odds ratio

Table G-2 The association of educational attainment with membership in patterns of cognitive state changes (Latin subsample, N = 368)

	Pattern[1] 1 vs 7	Pattern 2 vs 7	Pattern 3 vs 7	Pattern 4 vs 7	Pattern 5 vs 7	Pattern 6 vs 7
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Unadjusted						
Education (vs. ≤ high school)						
Bachelor's degree	1.10 (0.04–33.13)	2.57 (0.34–19.58)	1.93 (0.48–7.84)	3.89 (0.52–29.09)	1.10 (0.20–6.21)	2.23 (0.55–8.99)
≥ Master's degree	17.16 (0.68–433.86)	5.72 (0.72–45.67)	**6.64 (1.56–28.37)**	**9.88 (1.27–76.99)**	3.02 (0.51–17.67)	**4.33 (1.00–18.73)**
Adjusted for age and *APOE*						
Education (vs. ≤ high school)						
Bachelor's degree	1.59 (0.04–62.09)	2.47 (0.32–19.07)	2.01 (0.43–9.49)	3.61 (0.45–28.96)	1.07 (0.18–6.25)	2.00 (0.48–8.33)
≥ Master's degree	13.66 (0.41–457.19)	4.34 (0.54–36.94)	4.70 (0.94–23.57)	6.49 (0.77–54.89)	2.27 (0.36–14.24)	3.19 (0.70–14.58)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; OR = odds ratio

Table G-3 The association of educational attainment with membership in patterns of cognitive state changes (algebra subsample, N = 400)

	Pattern[1] 1 vs 7	**Pattern 2 vs 7**	**Pattern 3 vs 7**	**Pattern 4 vs 7**	**Pattern 5 vs 7**	**Pattern 6 vs 7**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Unadjusted						
Education (vs. ≤ high school)						
Bachelor's degree	2.05 (0.08–52.73)	3.61 (0.52–24.99)	2.83 (0.78–10.25)	5.36 (0.79–36.49)	1.70 (0.34–8.57)	2.27 (0.71 –7.24)
≥ Master's degree	**23.56 (1.02–546.42)**	**8.36 (1.14–61.26)**	**10.22 (2.64–39.48)**	**14.95 (2.09–106.67)**	4.71 (0.88–25.13)	**5.09 (1.46–17.66)**
Adjusted for age and *APOE*						
Education (vs. ≤ high school)						
Bachelor's degree	3.13 (0.10–97.09)	3.65 (0.52–25.52)	3.07 (0.74–12.66)	5.35 (0.75–38.01)	1.74 (0.34–9.03)	2.21 (0.68–7.24)
≥ Master's degree	20.49 (0.73–577.16)	7.34 (0.97–55.61)	**8.14 (1.83 –36.13)**	**11.71 (1.55–88.41)**	4.15 (0.74–23.39)	**4.35 (1.19–15.90)**

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; OR = odds ratio

Table G-4 The association of educational attainment with membership in patterns of cognitive state changes (geometry subsample, N = 385)

	Pattern[1] 1 vs 7	Pattern 2 vs 7	Pattern 3 vs 7	Pattern 4 vs 7	Pattern 5 vs 7	Pattern 6 vs 7
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Unadjusted						
Education (vs. ≤ high school)						
Bachelor's degree	2.02 (0.08–52.98)	3.36 (0.47–23.91)	2.59 (0.69–9.71)	5.28 (0.76–36.80)	1.21 (0.23–6.47)	2.11 (0.64–6.95)
≥ Master's degree	21.08 (0.89–497.59)	7.48 (1.00–55.86)	**9.44 (2.39–37.33)**	**13.37 (1.84–97.29)**	4.22 (0.77–22.95)	**4.34 (1.22–15.48)**
Adjusted for age and *APOE*						
Education (vs. ≤ high school)						
Bachelor's degree	2.30 (0.07–74.00)	3.02 (0.42–21.85)	2.32 (0.54–9.93)	4.58 (0.63–33.21)	1.08 (0.20–5.99)	1.91 (0.56–6.48)
≥ Master's degree	14.49 (0.49–424.19)	5.88 (0.75–45.82)	**6.49 (1.41–29.82)**	**9.46 (1.23–72.95)**	3.23 (0.55–18.81)	3.53 (0.93–13.34)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; OR = odds ratio

Appendix H

The association of academic performance with patterns of cognitive state changes

Table H-1 The association of academic performance in English or Latin with membership in patterns of cognitive state changes (English subsample, N = 401; Latin subsample, N = 368)

	Pattern[1] 1 vs 7	**Pattern 2 vs 7**	**Pattern 3 vs 7**	**Pattern 4 vs 7**	**Pattern 5 vs 7**	**Pattern 6 vs 7**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Unadjusted						
English	1.17 (0.57–2.41)	1.20 (0.68–2.11)	1.23 (0.80–1.91)	1.55 (0.93–2.59)	1.05 (0.59–1.89)	0.97 (0.63–1.50)
Adjusted for age and *APOE*						
English	1.24 (0.58–2.64)	1.26 (0.71–2.25)	1.31 (0.82–2.10)	1.65 (0.97–2.80)	1.11 (0.61–2.02)	1.02 (0.65–1.59)
Unadjusted						
Latin	0.97 (0.49–1.93)	1.07 (0.60–1.91)	1.06 (0.67–1.66)	1.31 (0.78–2.22)	0.78 (0.44–1.39)	0.85 (0.54–1.34)
Adjusted for age and *APOE*						
Latin	1.11 (0.54–2.28)	1.09 (0.61–1.97)	1.12 (0.69–1.82)	1.39 (0.80–2.41)	0.80 (0.44–1.45)	0.87 (0.55–1.39)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; OR = odds ratio

Table H-2 The association of academic performance in algebra or geometry with membership in patterns of cognitive state changes (algebra subsample, N = 400; geometry subsample, N = 385)

	Pattern[1] 1 vs 7	**Pattern 2 vs 7**	**Pattern 3 vs 7**	**Pattern 4 vs 7**	**Pattern 5 vs 7**	**Pattern 6 vs 7**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Unadjusted						
Algebra	1.01 (0.54–1.87)	**1.79 (1.03–3.10)**	1.24 (0.84–1.84)	**1.64 (1.03–2.62)**	1.32 (0.77–2.27)	1.17 (0.79–1.73)
Adjusted for age and *APOE*						
Algebra	1.11 (0.57–2.15)	**1.96** (**1.13–3.43**)	1.41 (0.92–2.15)	**1.83** (**1.12–2.97**)	1.48 (0.86–2.55)	1.25 (0.83–1.87)
Unadjusted						
Geometry	1.10 (0.57–2.11)	1.57 (0.89–2.79)	1.15 (0.76–1.74)	1.42 (0.88–2.31)	1.12 (0.63–1.98)	1.13 (0.74–1.73)
Adjusted for age and *APOE*						
Geometry	1.37 (0.67–2.81)	1.74 (0.98–3.11)	1.33 (0.85–2.08)	1.63 (0.99–2.65)	1.25 (0.70–2.25)	1.23 (0.80–1.89)

[1]Pattern 1) stable normal cognition, Pattern 2) stable mild cognitive impairment or stable global impairment, Pattern 3) decline and improvement without dementia, Pattern 4) progressive decline without dementia, Pattern 5) decline and improvement with dementia, Pattern 6) progressive decline with dementia, Pattern 7) stable dementia

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; OR = odds ratio