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EVALUATING LONGITUDINAL OUTCOMES OF COGNITION BY ENVIRONMENT, GENES, AND SLEEP IN AGING INDIVIDUALS

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To Marg for her support and encouragement in everything I do, for being my first and last reader and my always listener

and

To my mom, Karen McSorley, for her unwavering and endless support through all my endeavors, especially my academic endeavors. My mom's commitment to providing space and resources for people to thrive in their educational pursuits was borne out broadly in her career as a teacher and very specifically in my ability to complete this dissertation.

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ABSTRACT

Dementia and neurodegenerative diseases including Alzheimer's dementia (AD), which increase in prevalence with age, greatly impact the health and quality of life of older adults, as well as their families and support systems. At a population level, as the "Baby Boomer" generation enters older age, both the number and the proportion of older adults will continue to grow and along with it, the number of people with dementia and Alzheimer's disease. Some estimates project that by 2050, the prevalence of AD could grow three fold from levels in 2000 to as much as 13 million affected individuals[1,2] Identification of both preventable risk factors for dementia and Alzheimer's disease and for early indicators of decline is critical in intervention planning and in preparing healthcare and care infrastructures. Both level of cognition and rate of cognitive decline in mid and late life are predictive of the development of dementia. Prior research has identified behavioral, environmental, and genetic, namely the *APOE* ε4 allele, risk factors for cognitive function and decline and described pathophysiologic processes. Early indicators and many risk factors for cognitive decline are measured and represent temporally concurrent circumstances, but researchers have advocated for a life-course approach to studying cognitive aging[3,4] In this dissertation we used data from three cohorts to look at predictors of cognitive level, rate of decline, and of neuropathology associated with cognitive decline. Specifically, we aimed to 1) evaluate the association of actigraph and self-reported sleep with cognitive function and 5-year cognitive decline, 2) evaluate whether the genetic penetrance of the *APOE* ε4 risk allele varies by early life environment operationalized as birth-year cohort in one study and Adverse Childhood Experiences (ACEs) in another.

Sleep laboratory studies find that restricted sleep duration leads to worse short-term cognition, especially memory. However, sleep measured in the laboratory does not mirror the

regular sleep experiences of individuals in the home and laboratory study populations are often young and healthy adults. Thus, it is difficult to generalize these findings to older populations, who have more reports of sleep problems and who are at greatest risk for cognitive decline. Observational studies find associations between self-reported sleep duration or quality and cognitive function. However self-reported sleep characteristics may not be very accurate and misreporting could relate to cognition. Only a handful of observational studies have been able to combine self-reported sleep measures with actigraph measures of sleep patterns in older adults. We used data from the Sleep Study of the National Social Life, Health, and Aging Project (NSHAP), a nationally-representative cohort of U.S. older adults (2010-2015), to examine whether self-report and actigraph measured sleep were associated with cross-sectional cognitive function and 5-year cognitive decline. Cognition was measured with the survey adaption of the multidimensional Montreal Cognitive Assessment (MoCA-SA). At baseline (N=759), average MoCA-SA was 14.1 of 20 (SD 3.6). In cross-sectional models, actigraph sleep disruption measures (wake after sleep onset, fragmentation, percent sleep, wake bouts) were associated with worse cognition. Sleep disruption measures were standardized, and estimates of association were similar (range: -0.37 to -0.59 MoCA-SA point per SD of disruption). Actigraph sleep disruption measures were also associated with odds of 5-year cognitive decline (4 or more points), with wake after sleep onset having the strongest association (OR: 1.43, 95% CI: 1.04, 1.98). Longitudinal associations were generally stronger for men than women. Self-reported sleep showed little association with cognitive function.

To evaluate whether the relationship between the *APOE* ε4 risk allele and dementia related outcomes varies by early life environment, we used data from two cohorts: the Health and

Retirement Study (HRS) and the Memory and Aging Project (MAP) from the Rush Alzheimer's Disease Center.

The ApoE ε4 allele is a well-established genetic risk factor for Alzheimer's disease (AD). There is less consistent evidence as to whether the ε4 allele is associated with cognitive decline prior to, or in the absence of, AD. Heterogeneity between studies could be due to differences in study methods, such as type of cognitive assessment, or to the modification of the effect of the ε4 by other factors that vary between cohorts, such as socioeconomic background or ancestry. Gene by environment studies have tested for effect modification of the ε4 allele by environmental factors measured contemporaneous to cognitive assessment and by educational attainment. We evaluated whether birthyear cohort (an indicator of early life environment) was an effect modifier of the relationship between the ε4 allele and cognitive decline. HRS resurveys every two years and has enrolled six birthyear cohorts, which we combined into two: a prewar (b. 1894-1941) and a postwar (b. 1942-59) birth-year cohort. We used mixed-effects models with interactions to assess whether both level of cognitive function and rate of cognitive decline due to the ε4 allele varied between birth-year cohorts for individuals of the same age. We found that decline due to age in the postwar birth-year cohort was very similar regardless of ε4 status group (ε4 positive: β = -0.11, 95% CI: -0.13, -0.08, ε4 negative: β = -0.12, 95% CI: -0.13, -0.11). This was in contrast to the prewar birth-year cohort, where those with an ε4 allele had a much greater rate of decline over age (β = -0.21, 95% CI: -0.23, -0.20) compared to those without an ε4 allele (β = -0.15, -0.16, .0-14), leading us to conclude that the effect of possessing an ε4 allele was more strongly related to cognitive decline for those in the earlier born birth-year cohort, i.e. that the effect diminished over time. We also evaluated whether birth-year cohort differences were due to differences in educational attainment between the birth-year cohorts and did not observe

that this difference explained the finding. Differences in genetic penetrance across birth-year cohorts speak to broad changes in the environment beyond education that could be protective against genetic risk for cognitive decline.

In a complementary analysis, we used data from the Rush Memory and Aging Project to evaluate whether reports of Adverse Childhood Experiences modified genetic risk for cognitive function and decline as well as for neuropathology associated with dementia. ACEs address potentially traumatic experiences that happen during the first 18 years of life and have been associated with a variety of health outcomes in adulthood. There are five domains of ACEs: emotional neglect, parental intimidation, parental violence, family turmoil, and financial need. To identify patterning of ACEs, we used Latent class analysis to identify homogenous, mutually exclusive groups that we then interacted with presence/absence of an *APOE* ε4 risk allele to determine whether level of neuropathology or cognitive decline varied by latent class. We identified three classes and defined them as a low ACE class (Low), a middle class, defined by reports of emotional neglect and higher average reports of ACEs relative to the Low class (EN-Mid), and a class defined by high reports of all ACEs (High). Using mixed-effect models to model level and rate of cognitive decline over follow-up year, we did not find that ACE class membership modified the association of the *APOE* ε4 allele with cognitive function or decline. We also did not observe that ACE class modified the relationship of the *APOE* ε4 allele with primary AD pathology (neurofibrillary tangles, neuritic plaques, and diffuse plaques). However, we did observe that ACE class was independently associated with odds of gross chronic infarcts ($p=0.04$), driven by those in the EN-Mid group having a higher odds of showing evidence of infarct ($OR=1.67$, $p=0.01$), compared to the Low ACE group. In an interaction model, variation in penetrance of *APOE* ε4 allele by class membership was marginally significant ($p=0.06$). There

was trending evidence that having an *APOE* ε4 allele *and* being in the EN-Mid ACE class or High ACE class was associated with an increased odds of gross chronic infarcts, compared to the Low ACE class group ($OR_{EN\text{-}Mid+\varepsilon4}$: 1.73, 95% CI: 0.90, 3.32; $OR_{High+\varepsilon4}$: 4.43, 95% CI: 1.41, 13.39).

The final two aims conceptualize early life environment in two very distinct ways. The disparate findings highlight the importance of the variety of ways that we can think about how the early life environment may reach into older age to affect health outcomes.

INTRODUCTION

Cognitive decline and neurodegenerative diseases including Alzheimer's dementia (AD), which increase in prevalence with age, greatly impact the health and quality of life of older adults, as well as their families and support systems. As our populations ages, more and more older adults and their families will experience cognitive decline and potentially clinical manifestations of impairment and dementia. Prior research has identified behavioral, environmental, and genetic risk factors for cognitive decline and described pathophysiologic processes. Individual level factors such as cardiovascular disease, health behaviors such as smoking and level of physical activity, and genetic polymorphisms have all been implicated in later life cognitive outcomes and neurodegenerative disease. More distal factors have also been identified, such as educational attainment, SES throughout the life course, and cognitive engagement throughout the life course.

This dissertation will explore relationships between genes, individual level environment, population level environment, and behavioral factors with cognitive health outcomes.

Sleep and Cognition

Several studies have observed associations between sleep and cognition. The strongest and most consistent findings have been in laboratory studies that have demonstrated a clear relationship between sleep and performance in memory related tasks.[5–9] Studies have also demonstrated relationships between sleep and other cognitive domains including language, visuospatial ability, and decision-making, though findings have been less consistent (for review see Alhola, 2007).[10] However, these studies have all been lab based and have manipulated sleep by restriction.

While compelling, sleep that is measured or manipulated in laboratory environments hardly mimics sleep in the home environment or sleep patterns among individuals who do not participate in laboratory sleep studies. As such, survey research has sought to assess the relationship between sleep characteristics among community dwelling individuals and cognition. Indeed, associations have been observed between sleep and cognition in survey-based research. However, many of these studies have relied on self-report of nighttime sleep duration and daytime sleepiness – constructs which have low correlation with both laboratory-measured polysomnography and sleep characteristics measured via wrist actigraphy.[11–13] Additionally, self-report of nighttime sleep, in particular, could be a cognitively burdensome question if respondents are asked to calculate how many hours they sleep each night, which has the potential to introduce bias in that the measurement of the exposure could be correlated with the outcome.

These limitations have also been recognized and, as such, a handful of studies have been conducted to assess the relationship between sleep and cognition using actigraphy, considered to be a more objective measure of sleep characteristics and variation in sleep patterns. Furthermore, the studies which have sought to evaluate the relationship between actigraph measured sleep and cognition have been studies of older adults, the very population who experiences poorer quality sleep and is at highest risk for cognitive impairment. In the Study of Osteoporotic Fractures, actigraph-measured sleep disruption measures including low sleep efficiency and high wake after sleep onset (WASO) were associated with cognitive impairment, as was high sleep latency.[14] However, this study was cross-sectional so directionality of the relationship cannot be determined. It was also conducted solely among older women. In a similar study conducted among only men, WASO was also associated with cognitive impairment in a cross-sectional

setting.[15] This study was followed up and a longitudinal analysis also saw associations between WASO and another sleep disruption measure, number of long wake episodes, and increased cognitive decline.[16] Both of these studies used the Mini-Mental State Exam (MMSE) as their measure of cognitive function. While the MMSE was once widely used in population based surveys to assess transitions to severe cognitive impairment and dementia, it has waned in implementation due to its low sensitivity to detecting more mild cognitive impairment or subtle changes in cognition, which may be more important changes in cognitive function particularly for the non-institutionalized aging population.[17–19]

Aim 1 seeks to build on this body of knowledge by assessing the relationship between actigraph measured sleep characteristics and changes in cognitive performance among community dwelling older adults over a 5-year period.

Aim 1 Innovation

This is the first study to assess the relationship between actigraph measured sleep and cognition in a population drawn from a nationally representative sample of community dwelling older adults. Actigraph measures sleep is less subject to bias than self-reported sleep measures and is less invasive and disruptive to actual sleep than polysomnography. Additionally, the measure of cognition used in this survey (Montreal Cognitive Assessment – Survey Adapted) is more sensitive to subtle changes in cognition and to mild cognitive impairment than previously implemented survey measures.

Gene by Early-Life Environment

Among genetic risk factors, the Apolipoprotein E (*APOE*) ε4 allele is the most established for Alzheimer's disease[20–22] and has also been shown to be associated with dementia, cognitive decline and progressive memory loss.[23–26] Yet, risk of dementia and cognitive decline

varies for those with one and two ε4 alleles, indicating that other risk factors, including other genes, other individual level factors, or environments, could modify the relationship between *APOE* and cognitive outcomes.[23,27]

Among non-genetic social factors, there is a substantial body of research exploring the relationship between early-life circumstances and late-life health outcomes, including cognition. In particular, early-life socioeconomic level at home[28,29] and in the community[30], cognitively stimulating activity in early childhood[31,32], and adversity in childhood[33] have been associated with late-life neurological conditions including mild cognitive impairment, Alzheimer's, and dementia.

Considering larger social context, in the past century, we have seen an increase in overall socio-economic status in the United States, exemplified by higher levels of education attainment and broader access to educational opportunities. Recent evidence has indicated that in developed countries, the age-adjusted prevalence of these neurocognitive conditions may also be leveling off or declining, as well.

Studies have been conducted to assess whether socio-environmental conditions may moderate the effect of genetic polymorphisms on late-life cognitive outcomes. Most studies have looked at variation in the penetrance of genetic variants on cognitive outcomes by individual educational attainment or by social and environmental measurements taken proximal to the onset of cognitive decline, (i.e. adult or late-life SES and/or cognitively engaging activity). These studies have considered whether genetic variants could act as modifiers in the relationship between the environment and cognitive decline. There is evidence that genetic penetrance of variants associated with cognitive function varies by engagement in cognitively stimulating activities in adulthood and older ages, physical activity in adulthood and older ages, and

education achieved.[34–39] However, there is less evidence as to whether this variation in genetic penetrance can be seen by variability in early-life circumstance, measured either at the individual or population level.

There is a vast and growing literature that demonstrates that the early-life environment is associated with a broad range of late-life health outcomes, including cognition. In a lifecourse perspective, studies have demonstrated relationships between early-life environment (often proxied by birth-year cohort) and late-life cognitive outcomes. Forsdahl[40] demonstrated that poverty in childhood, operationalized as birth cohort-wide infant mortality rates, was associated with increased mortality due to heart disease, despite cohort-wide economic growth. Case and Paxson[41] used cohort-wide infant mortality as a measure of early-life disease burden and observed that high rates were associated with lower performance on cognitive tests in older age. Doblhammer et al[42] found that periods of economic recession in Europe were associated with lower average cognitive function in older age. Broadly, age-adjusted average cognition and incidence of neurodegenerative diseases favor later born cohorts.[43–46] These improvements have been attributed to increasing access to and quality of education and changes in fetal or early-life circumstances characterized by differences in economic, social, nutritional, and disease environments. At the individual level, early-life socioeconomic level at home and in the community,[28–30] cognitively stimulating activity in early childhood,[31,32] and adversity in childhood[33,47] have been associated with late-life cognitive status. What remains unknown is to what extent early-life environment influences the penetrance of cognitively associated genes later in life.

Modification of the risk attributed to the *APOE* ε4 allele on cognitive pathology could occur via neuropathology or via cognitive resilience despite neuropathology, a mechanism also

known as development of cognitive reserve.[48] There is evidence that higher early-life cognitive ability is associated with decreased late life neuropathological burden[49]. However, other environmental measures, such as level of education, have not shown any associations with neuropathology, and instead appear to influence cognitive capacity despite accumulation of AD related neuropathology, i.e. by creating cognitive reserve.[50]

Aims 2 and 3 of this dissertation are designed to address the gaps in the literature, using complementary cohort studies, the Health and Retirement Study (HRS) and the Memory and Aging Project (MAP) of the Rush Alzheimer's Disease Center (RADC) Cohorts.

Innovation

The innovation in this proposal is three-fold. First, this research contributes to the small set of studies (all with other health outcomes) considering potential change in penetrance of genes over time (i.e. by birth-year cohort).[51–54] Second, while other studies have looked at GxE interactions on cognition in older adults, this will be among the limited scholarship addressing whether the cognition associated risk alleles vary in effect by early-life environment. Third, this research seeks to bring together analyses from two cohorts with complementary strengths. HRS is a nationally representative, population-based longitudinal panel study, it is the gold standard for such studies in the U.S. aging population, with a large sample size and repeated survey measures. The MAP represents a strong epidemiological cohort investigating the etiology of a specific disease with state-of-the art clinical measures of cognition and neuropathology, in carefully-chosen populations.

SLEEP CHARACTERISTICS AND COGNITIVE FUNCTION AND DECLINE AMONG OLDER ADULTS

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Abbreviations in Manuscript:

CI – Confidence Interval

MCI – Mild Cognitive Impairment

MMSE – Mini-Mental State Exam

MoCA-SA – Montreal Cognitive Assessment – Survey Adapted

MrOS – Osteoporotic Fractures in Men Study

NSHAP – National Social Life, Health, and Aging Project

OR – Odds Ratio

SD – Standard Deviation

SOF – Study of Osteoporotic Fractures

TST – Total Sleep Time

WASO – Wake after sleep onset

ABSTRACT

Sleep laboratory studies find that restricted sleep duration leads to worse short-term cognition, especially memory. Observational studies find associations between self-reported sleep duration or quality and cognitive function. However self-reported sleep characteristics may not be very accurate and misreporting could relate to cognition. In the Sleep Study of the National Social Life, Health, and Aging Project (NSHAP), a nationally-representative cohort of U.S. older adults (2010-2015), we examine whether self-report and actigraph measured sleep are associated with cross-sectional cognitive function and 5-year cognitive decline. Cognition is measured with the survey adaption of the multidimensional Montreal Cognitive Assessment (MoCA-SA). At baseline (N=759), average MoCA-SA was 14.1 of 20 (SD 3.6). In cross-sectional models, actigraph sleep disruption measures (wake after sleep onset, fragmentation, percent sleep, wake bouts) were associated with worse cognition. Sleep disruption measures were standardized, and estimates of association were similar (range: -0.37 to -0.59 MoCA-SA point per SD of disruption). Actigraph sleep disruption measures were also associated with odds of 5-year cognitive decline (4 or more points), with wake after sleep onset having the strongest association (OR: 1.43, 95% CI: 1.04, 1.98). Longitudinal associations were generally stronger for men than women. Self-reported sleep showed little association with cognitive function.

Keywords: cognition, sleep, actigraphy, cohort study

Abbreviations: NSHAP, National Social Life, Health, and Aging Project; MoCA-SA, Montreal Cognitive Assessment – Survey Adapted; SD, standard deviation; OR, odds ratio; CI, confidence interval

INTRODUCTION

Observational and experimental studies have found associations between sleep and cognitive function. The strongest and most consistent findings have been in experimental studies demonstrating a clear relationship between restricted sleep in a laboratory setting and next day short-term performance in memory related tasks[5–9] Lab-based studies have also demonstrated relationships between sleep deprivation and other cognitive domains including language, visuospatial ability, and decision-making, though findings for these have been less consistent (Alhola, 2007 [10], review).

Sleep manipulated in laboratory environments differs by design from home sleep patterns, and there may be systematic differences between laboratory study volunteers, generally healthy, young, and paid adults in the community. Observational studies also demonstrate relationships between self-reported sleep characteristics among community-dwelling individuals and cognitive function.[55–58] However, survey responses on sleep duration have low to moderate correlation with sleep characteristics objectively estimated either by polysomnography or wrist actigraphy.[11–13] Reporting sleep duration could be cognitively challenging, as accurate answers require determining usual bedtime and waking time, which may have daily variation, and performing mental arithmetic, often around midnight. Additionally, inaccurate reporting has been linked to health determinants, including socioeconomic indicators, raising the possibility that associations between self-reported sleep and health outcomes may be biased.[12]

To address limitations of self-reported sleep characteristics, a few cohorts have added objective measures. For research about cognitive function, older adults are the population of greatest interest because they have highest risk for cognitive decline and report worse sleep.[59] Two cohorts objectively measuring sleep have found associations between actigraphic indicators

of poor sleep and cognitive impairment: the female-only Study of Osteoporotic Fractures (SOF) and the male-only MrOS.[15,16,60,61] Findings differed somewhat between the studies, suggestive of possible gender differences in the sleep-cognition relationship. Both cohorts used the Mini-Mental State Exam (MMSE) and the Trails B as measures of cognitive function. The Trails B is a test of executive function and the MMSE is a widely screener for severe cognitive impairment and dementia, but has low sensitivity for mild cognitive impairment (MCI) or tracking moderate changes.[17–19]

In this study, we use a nationally-representative cohort study of older adults that included a multi-domain cognitive assessment sensitive to MCI to assess (1) cross-sectional associations between actigraph and self-reported sleep characteristics with cognitive function; and (2) longitudinal associations between sleep and five-year decline in cognitive function. We examine whether associations differ for actigraphy and survey measures and investigate gender interactions.

METHODS

Study Population

The National Social Life, Health, and Aging Project (NSHAP) is a nationally-representative study of community-dwelling older adults born between 1920 and 1947 which has fielded three waves: in 2005/06, 2010/11, and 2015/16. In Wave 2, spouses and co-resident partners of original cohort members were invited to participate. Each wave included in-home interviews and biomeasures. The NSHAP Sleep Study is a substudy that began in Wave 2. A randomly-selected one-third of Wave 2 respondents (n=1,117) were asked to participate, wearing a wrist actigraph for 72 hours (three nights) and answering additional questions in a booklet.

Those alive 5 years later were recontacted as part of Wave 3. Here, we refer to the Wave 2 Sleep Study as "baseline" and Wave 3 as "follow-up".

Selected cohort members were asked if they would participate in the Sleep Study during the in-home interview, but the protocol required they be recontacted to arrange delivery of materials. Of 1,117 respondents who were asked to participate, 897 initially agreed. Among them, 823 were successfully recontacted in the available timeframe, and 801 returned usable sleep data (returning either an actigraph watch with recorded data or a sleep booklet with responses – see Figure 1).

We included participants who had at least one night of actigraph data. This analysis is limited to those born between 1920 and 1947 (n=759) (See Figure 1), the initial birth year range. Agreement to participate in the Sleep Study and return of actigraphy data were not themselves related to cognitive function.[62]

Of those with sleep data, 24.2% were not re-interviewed at the 5-year follow-up due to death, poor health, or other reasons (Figure 1). Thus cross-sectional results include 759 participants and longitudinal results include 555.

Wrist Actigraphy

Collection of the sleep data has been fully described elsewhere.[63] Participants were instructed to wear the wrist actigraph (Actiwatch Spectrum model from Phillips Respironics) for 72 hours. The Actiwatch was set to record activity data in 15-second epochs. When the device was returned, data were downloaded and analyzed, using Phillips Respironics software (version 5.59) and their validated settings.[63]

A participant's rest intervals were first set by the software, based only on the activity pattern. Then each record was reviewed by the investigators and rest intervals revised based on

additional information that the software did not use: the participant-initiated event marker time stamp that they were asked to press at each bedtime and waking time and the light sensor on the actigraph. Overall, the event marker was pressed 84% of the total nights analyzed.[63] The software scores each 15-second epoch as sleep or not based on activity counts in that epoch and surrounding epochs. The sleep interval is the period within each rest interval beginning with the first epoch scored as sleep and ending with the last epoch scored as sleep.

Sleep measures used in this study are all calculated within the sleep interval: total sleep time (TST – summed duration of all epochs scored as sleep); wake after sleep onset (WASO – summed duration of all epochs scored as wake); sleep fragmentation (the sum of the percent of epochs with any motion – which may or may not be scored as sleep -- and the percent of immobile periods less than one minute long); percent sleep (TST divided by the sleep interval); and number of wake bouts (distinct series of contiguous epochs scored as wake). Sleep measures were calculated as an average over the number of nights (mean=2.84 nights, SD=0.56). Additionally, we categorized individuals into diurnal types (24, 25) using the average midpoint of their sleep intervals, divided into three categories (10pm-1:59am, 2am-2:59am, and 3am-8:59am), which included all participants.

Survey Sleep Data

The Sleep Study booklet asked "How many hours do you usually sleep at night?" and the frequency of three insomnia symptoms: trouble falling asleep, waking up during the night, and waking up too early and not being able to fall asleep again. Responses were "rarely or never," "sometimes," or "most of the time." These responses (coded 0, 1, or 2) were combined with a NSHAP core question on frequency of feeling rested upon waking in the morning (reverse

coded) to create a scale of insomnia symptoms ranging from 0 to 8, with a higher score indicating more insomnia symptoms.

Cognition

Cognitive function was measured using the Montreal Cognitive Assessment (MoCA)[66] adapted for survey administration (MoCA-SA).[17,67] The MoCA was developed as a cognitive screening tool for use in clinical practice to assess MCI across key cognitive domains and has a 90% sensitivity in detecting clinically diagnosed MCI[66] The MoCA-SA is highly correlated (r=0.97) with the full MoCA.[17,67] The MoCA-SA includes 11 items measuring eight domains: orientation, naming, visuo-construction, executive function, attention, abstraction, memory, and language. The score on the MoCA-SA ranges from 0 to 20. It was administered in each wave, in English or Spanish.

Other Measures

Demographics included age (continuous), gender, race/ethnicity, and education.

Other risk factors for cognitive impairment included frailty, depression, a comorbidity index, medications, alcohol use, body mass index, napping, frequent physical activity, and sleep apnea (at follow-up only). The frailty scale includes four of the five physical criteria proposed by Fried and colleagues:[68] weak grip strength, slow gait, exhaustion, and low physical activity. We omitted unintentional weight loss, the fifth criterion, because we do not have prior measured weight for spouses and partners enrolled for the first time in Wave 2.[69] This generated a four-point scale, with higher points indicating greater frailty. Depression was measured using an 11-item short form of the Center for Epidemiologic Studies Depression Scale which generated a score with a range of 0-22, with higher scores indicating greater depressive symptomology.[70] We used a modification of the Charlson Comorbidity Index developed for NSHAP, which includes

10 of the 19 conditions in the full index. The modified index creates a scale with a range of 0 to 16 and is highly correlated with the full index ($r = 0.89$).[71] Indicators for current usage of medications include prescription antidepressants and both prescription and non-presciption sleep aids including anxiolytics, sedatives, and hypnotics. For the follow-up wave, a question was added asking if participants had ever been diagnosed with sleep apnea.

Participants were asked about napping in the sleep booklet. They were asked to record the total time they spent napping each of the three days in the following categories: no nap, less than 15 minutes, 15 minutes to 1 hour, or more than 1 hour. We used the duration midpoints from the responses to estimate nap length to four categories (0, 7.5, 37.5, 90 minutes) and averaged over the 3 days.

Statistical Analysis

We present demographic, risk factor, and sleep characteristics for the Sleep Study baseline and those with five-year follow-up.

We standardized the actigraph disruption measures (WASO, fragmentation, percent sleep, and number of wake bouts) to facilitate comparisons. For the cross-sectional analyses, we used linear regression to assess the association between each sleep parameter and MoCA-SA at baseline, adjusted for demographics and then added risk factors for cognitive impairment.

To examine five-year cognitive change, we focused on those with a clear decline. At follow-up, 43 percent had a score that was the same or within one point of their baseline score, and 20 percent increased by two or more points, suggestive of a learning effect. We dichotomized cognition scores at the cut point which most closely represented the lowest quintile, a decline of 4 or more points. We used logistic regression to examine associations between sleep characteristics and cognitive decline, first adjusted for demographics, then adding

risk factors for decline. We include sleep apnea diagnosis as a risk factor in the decline models, but not cross-sectional models, as it was only assessed at follow-up. We also tested for gender interactions with sleep measures.

We provide five sensitivity analyses in the web material, (1) assessing selection bias due to loss to follow-up using the inverse Mills' ratio,[72] (2) using a threshold for cognitive decline of 3 points instead of 4, (3) excluding individuals reporting Alzheimer's or dementia diagnoses at baseline, and (4) a cross-sectional model only including those with follow up data in order to adjust for sleep apnea. We also consider (5) a model using just one insomnia item, trouble waking during the night, as a more direct comparison to WASO than the four-item scale.

We evaluated spousal correlation using multilevel models clustering on household id, but did not find any correlation after adjustment for demographics in our baseline model. As such, all analyses took into account the study design and sampling weights to account for the complex survey design and nonresponse.[73] All data were analyzed using Stata Version 15.1 (StataCorp LP, College Station, TX).

RESULTS

Table 1 shows baseline characteristics for all participants and for those included in the follow-up assessment. Both younger and female participants were more likely to survive to follow-up. Race/ethnicity and education were similar for the full baseline cohort and those with follow-up.

Table 2 shows actigraph and self-report sleep characteristics and MoCA-SA scores at baseline and at baseline for those with follow-up. At baseline, the average MoCA-SA score was 14.1 (SD: 3.6); those with follow-up had a slightly higher baseline average (14.7, SD: 3.3).

Cross-sectional Associations Between Sleep and Cognition

All four actigraph measures of sleep disruption were significantly associated with cognition, adjusted for demographics and for additional risk factors (Table 3). More disrupted sleep was associated with a lower MoCA-SA score. WASO was the most strongly associated with cognition, with a 1 SD (22.5 minutes) increase in WASO associated with a 0.59 point lower MoCA-SA score (95% CI: -0.85, -0.33). Diurnal phase was not associated with cognition. There was no evidence of a linear association between TST and MoCA-SA score, or suggestion of a U-shaped association.

There was no evidence of a linear association between self-reported sleep duration and MoCA-SA, although those reporting shortest sleep (<6 hours) had higher average MOCA-SA score. There was no evidence of an association for insomnia symptoms.

Sleep and 5-year cognitive function decline

In the demographic-adjusted models (Table 4), WASO and percent sleep were significantly associated with odds of cognitive decline, and fragmentation trended in the same direction. Number of wake bouts was not associated with decline. Further adjustment for risk factors had little effect on the odds ratio estimates for WASO, fragmentation, and sleep percent. There was also some evidence that earlier circadian timing (sleep midpoint between 8pm to 1:59am) was associated with higher risk of decline, compared to those with later circadian timing (OR: 2.22, 95% CI: 0.89, 6.18). Those with low actigraph measured TST (<6h) had increased odds of cognitive decline, compared to those sleeping 7-8h (OR: 3.41, 9% CI: 1.19, 9.76). Self-reported short sleepers trended in the same pattern. Insomnia was not associated with odds of decline.

In the gender interaction models, there was no evidence for different cross-sectional associations (data not shown), but there was evidence that the associations between sleep disruption and cognitive decline were stronger among men than among women (Table 5). Interaction terms were significant for sleep fragmentation and number of wake bouts, and there was a pattern of gender difference for WASO and percent sleep. There was qualitative interaction for wake bouts, such that more wake bouts increased the odds of cognitive decline for men but decreased the odds of decline for women.

In sensitivity analyses for selection, the inverse Mills' ratio was not significant in any of the selection models. It slightly attenuated our observed measures of association but did not change the pattern of results (Web Table 1). None of our sensitivity analyses substantively changed measures of association (Web Tables 2-5).

DISCUSSION

In a nationally representative cohort of older men and women, we found that actigraph measures of sleep and self-reported measures of sleep have different cross-sectional and longitudinal associations with cognitive function and decline. We found actigraph measures of sleep disruption and quality are negatively associated with cognition measured concurrently and are associated with 5-year cognitive decline. In the cross-sectional analysis, this association did not differ between men and women, but actigraph measures of sleep disruption were more strongly associated with 5-year cognitive decline among men compared to women. Short actigraph TST was associated with higher odds of cognitive decline, but there was no evidence of a linear or U-shaped association across the full range of TST. We did not find that self-reported sleep quality (insomnia symptomology) was associated with worse cognition or cognitive decline. Perceptions of sleep duration were also unrelated to cognitive function and

decline. We found some evidence that earlier diurnal phase might be associated with greater 5-year decline. Diurnal phase is a measure of circadian rhythm, and this is often shifted earlier for older adults.[65] The observed associations are consistent with sleep disruption and potentially circadian phase shift playing a causal role in cognitive decline or with there being an underlying biological process that predisposes older adults to both. However, in the Study of Osteoprortic Fractures (SOF), peak activity occurring later in the day was associated with increased incidence of MCI/dementi.[74] This difference could be due to our defining circadian phase using the mid-point of sleep, or it could be due to the age difference between women in NSHAP and in SOF.

Unlike much of the previous sleep literature, we do not find that reported sleep duration or insomnia symptoms are related to cognitive function or decline.[55–58]However, our findings are broadly consistent with results from the SOF and the study of Osteoporotic Fractures in Men (MrOS). In both studies, WASO was associated with concurrent cognitive impairment on both the Trails B and the MMSE.[15,61] In SOF, low sleep efficiency (TST divided by the rest interval) was also associated with lower cognitive scores on both tests of cognitive function.[61] The association between sleep disruption and cognitive decline we observe is also observed in MrOS, where WASO, low sleep efficiency and the number of long wake episodes were associated with greater cognitive decline over an average of 3.4 years on the MMSE and the Trails B.[16] A comparable association was not seen in SOF on neither the Trails B nor the MMSE (personal communication with Katie Stone, University of California, San Francisco, March 1, 2018). However, in a follow-up study among a subsample of SOF participants who were given an extensive battery of clinician-reviewed cognitive tests; low sleep efficiency and longer sleep latency (time between the beginnings of the rest interval and the sleep interval) were associated with incident MCI/dementia.[60] Of note, the average age of participants in SOF (87.4 years and

82.6 years in the substudy) and MrOS (76 years) was older than the participants in the current study (71.9 years).[15,16,60,61]

The report of different longitudinal associations in MrOS (male cohort) and SOF (female cohort) does not necessarily imply a different effect for men and women, as there are differences besides gender between the two cohorts, including the age distributions at the time of analyses. However, we observe significant differences between men and women in the NSHAP Sleep Study. The reasons for these differences are unknown, although a greater prevalence of obstructive sleep apnea in men versus women could play a role, as apnea has also been associated with cognitive impairment.[75,76] Indeed, in our sample, men had a higher prevalence of apnea than women at follow-up (21% vs. 10%). However, we do adjust for apnea in the longitudinal model. While a number of studies have reported differences in sleep characteristics between men and women,[77–79] there has been limited research on whether the effects of sleep differ by gender. The studies that do assess this difference are often among younger populations,[80,81] rely on self-reported sleep,[82,83] or deal specifically with sleep apnea as opposed to non-clinical variation in sleep.[84,85] We believe our study is the first to report differential associations of sleep on a health outcome by gender using objective measures of sleep in a community-based sample of older adults.

A key strength of this study is the measure of cognitive function. Unlike cognitive assessments in many omnibus surveys, the MoCA-SA is a validated multi-domain assessment developed to assess and track mild cognitive impairment.[17] Additionally, NSHAP's national sampling frame allows results to be generalized to the US population of community-dwelling older adults born between 1920 and 1947. Use of wrist actigraphy allows us to compare observed associations with self-perceptions of sleep duration and quality. While many studies have

considered the relationship between self-reported sleep characteristics such as insomnia symptoms and sleep duration with cognition, discrepancies between self-reports of sleep and more objective measures may be pronounced in older populations.[11,86–88] Our relatively small sample size is a limitation that must be acknowledged. Findings of marginal statistical significance may reflect, in part, the sample size and insufficient statistical power to detect associations. We did not carry out an analysis of incident MCI or dementia among those with neither at baseline because that would have further reduced the sample size. While actigraphy estimates sleep from arm motion as opposed to direct measurement of brain activity, it is generally considered a valid and useful approach to objectively estimating sleep characteristics without itself affecting sleep behavior.[89] More than three days of actigraphy are recommended to assess sleep patterns, particularly to capture variation between workdays and weekends. However, we have found little day-of-the-week effect in this cohort of older adults.[63]

Prior evidence that sleep characteristics are indicators of future cognitive decline among older adults has relied mainly on self-reported sleep characteristics. Previous studies focus on sleep duration as an important contributor to cognitive function, with self-reported short and long durations indicative of higher risk for cognitive decline.[56,58] In contrast to previous studies, we did not find evidence that self-reported sleep duration was a significant contributor to cognitive function. These results call into question the usefulness of self-reports of sleep as measures of sleep pertinent to cognitive function. Similarly, there appears to be no evidence that insomnia is a risk factor for cognitive decline, which may be reassuring for the many older adults who report insomnia symptoms. We have shown here that measured sleep disruption is a more important aspect of sleep than duration for predicting cognitive decline. Our findings add to the evidence that sleep disruption and quality measured using wrist actigraphy are salient dimensions of sleep

when considering the relationship between sleep and cognitive function at older ages. Further, we have shown that this association may be stronger among men than among women, but that unexplained finding needs replication.

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CITATION

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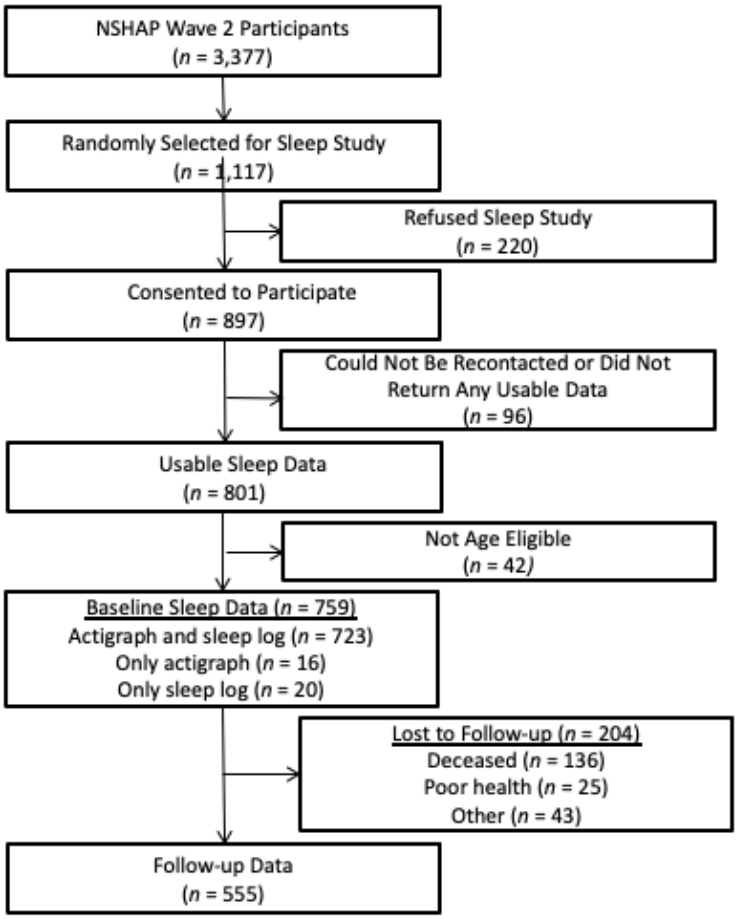
Figure 1.1: Flow Chart of Participants in the NSHAP Sleep Study (United States, 2010-2015).



*Among those who returned actigraph watches with usable data, 93% recorded 3 nights of sleep. Another 6% recorded 2 nights and 1% recorded 1 night. We included all participants who had any actigraph data.

Table 1.1: Baseline Characteristics of NSHAP Sleep Study Participants (United States, 2010-2015), for All Participants and for those Included in the 5-year Follow-up.

Characteristic	All (n=759)		Participants with Follow-up (n=555)	
	%	Mean (SD)	%	Mean (SD)
Age		71.9 (7.3)		70.5 (6.6)
Female	54.0		57.7	
Race/Ethnicity				
White	82.3		82.6	
Black	7.5		7.7	
Hispanic	6.8		6.5	
Other	3.4		3.3	
Education				
<High School	14.5		13.2	
High School	24.4		25.3	
Some College	37.2		36.7	
College Degree or Higher	24.8		24.8	
Modified Charlson Comorbidity1		1.1 (1.4)		0.9 (1.2)
0	44.9		49.5	
1	27.2		26.7	
2	15.3		15.1	
3	7.1		5.2	
>4	5.5		3.4	
Frailty (range:0-4)2		1.1 (1.2)		1.1 (1.2)
Depression (range: 0-22)3		7.6 (3.4)		7.5 (3.4)
Medication Usage				
Antidepressants	17.2		16.7	
Sleep Aids	8.9		8.9	
Alcohol Use (> 4 days/week)	12.4		12.3	
Body Mass Index				
Underweight	<1.0		<1.0	
Normal	24.7		22.9	
Overweight	35.3		36.4	
Obsese	39.6		40.3	
Physical Activity >=1/week	43.4		45.0	
Daytime Naps (min)		15.0 (20.9)		12.8 (18.5)
Sleep Apnea	Not assessed		14.6%	

[1]Modified Charlson Comorbidity scale includes: heart condition, stroke, cancer, diabetes, hypertension, arthritis, bone fractures/osteoarthritis, COPD/asthma, Alzheimer's disease/dementia, incontinence
[2]Frailty scale: weak grip strength, slow gait, exhaustion, and low physical activity
[3]Depression: 11-item short from of the Center for Epidemiologic Studies Depression Scale

Table 1.2: Sleep Characteristics and MoCA-SA Scores for Participants in the NSHAP Sleep Study (United States, 2010-2015) at Baseline, and for those with 5-year Follow-up.

Sleep Characteristic	All (n=759)		Participants with Follow-up (n=555)	
	%	Mean (SD)	%	Mean (SD)
	Actigraph Measured Sleep Characteristics			
WASO (minutes)		38.7 (22.5)		36.5 (19.6)
Fragmentation		14.4 (6.0)		13.8 (5.5)
Total Sleep Time				
<6 hours	13.8		13.1	
6 - 6.99 hours	27.5		28.3	
7 - 7.99 hours	34.6		35.2	
8 - 8.99 hours	17.1		17.1	
>= 9 hours	6.9		6.3	
Percent Sleep		91.8 (0.04)		92.2 (0.04)
Wake Bouts (number)		45.8 (21.6)		44.9 (20.2)
Diurnal Phase				
8pm-1:59am	21.6		20.8	
2am-2:59am	36.0		37.4	
3am-8:59am	42.5		41.8	
	Self-Reported Sleep Characteristics			
Self-Report Hours				
<6 hours	7.6		7.9	
6 - 6.99 hours	16.0		15.5	
7 - 7.99 hours	25.3		27.5	
8 - 8.99 hours	32.2		32.5	
>= 9 hours	19.0		16.7	
Insomnia Symptom Score (Range: 0-8)		2.8 (2.1)		2.8 (2.1)
	Cognitive Score			
MoCA-SA Baseline		14.1 (3.6)		14.7 (3.3)

Abbreviations: WASO, wake after sleep onset; MoCA-SA, Montreal Cognitive Assessment – Survey Adapted

Table 1.3: Associations between Baseline Sleep Characteristics and Baseline MoCA-SA in the NSHAP Sleep Study (United States, 2010-2015) from OLS Regression Models.

Model[1]	Individual Sleep Parameters	Demographic Adjusted Models[2] (N=732)			Risk Factor Models[3] (N=575)		
		Coef.	95% CI	p-value	Coef.	95% CI	p-value
	Actigraph Measured Sleep Characteristics						
1	WASO[4]	-0.59	-0.85, -0.33	<0.01	-0.55	-0.83, -0.27	<0.01
2	Fragmentation[4]	-0.50	-0.74, -0.26	<0.01	-0.39	-0.66, -0.13	<0.01
3	Sleep Percent[4]	0.46	0.21, 0.71	<0.01	0.37	0.11, 0.63	0.01
4	Wake Bouts[4]	-0.37	-0.61, -0.12	<0.01	-0.40	-0.67, -0.13	<0.01
5	Diurnal Phase[5]						
	8pm-1:59am	0.06	-0.60, 0.73	0.85	0.30	-0.41, 1.00	0.41
	2am-2:59am	0			0		
	3am-8:59am	0.01	-0.54, 0.56	0.98	0.19	-0.43, 0.82	0.54
6	Total Sleep Time						
	<6 hours	-0.01	-0.78, 0.77	0.98	0.34	-0.50, 1.17	0.43
	6 - 6.99 hours	-0.19	-0.78, 0.40	0.53	-0.11	-0.76, 0.55	0.75
	7 - 7.99 hours	0			0		
	8 - 8.99 hours	-0.09	-0.79, 0.61	0.80	0.00	-0.74, 0.73	0.99
	>= 9 hours	-0.74	-1.72, 0.25	0.14	-0.71	-1.72, 0.31	0.17
	p for trend	0.61			0.21		
	Self-Reported Sleep Characteristics						
7	Self-Report Hours						
	<6 hours	-0.74	-1.39, -0.08	0.03	-0.37	-1.15, 0.40	0.34
	6 - 6.99 hours	-0.56	-1.46, 0.34	0.23	-0.38	-1.43, 0.67	0.48
	7 - 7.99 hours	0			0		
	8 - 8.99 hours	-0.11	-0.73, 0.50	0.72	0.24	-0.43, 0.90	0.48
	>= 9 hours	-0.58	-1.37, 0.22	0.15	-0.14	-0.93, 0.66	0.74
	p for trend			0.32			0.23
8	Insomnia Symptoms[6]	0.01	-0.11, 0.12	0.92	0.05	-0.08, 0.17	0.47

Abbreviations: WASO, wake after sleep onset

[1]Model numbers indicate separate models

[2]Demographic adjusted models include age, gender, race/ethnicity, and education

[3]Risk factor models additionally include frailty, depression, modified Charlson Comorbidity Index, sleep aids, antidepressants, alcohol use, daytime napping, physical activity, and BMI

[4]Continuous sleep parameters are standardized

[5]Calculated from the average midpoint of sleep interval over three nights of actigraphy

[6]Range: 0-8 – a combined metric (0 = Never/rarely, 1 = Sometimes, 2 = Most of the time) from four questions: feeling rested in the morning, trouble falling asleep, trouble waking during the night and trouble waking too early. In the risk-adjusted models for the Troubled Sleep Scale, the depression scale, CES-D, does not contain the restless sleep item.

Table 1.4: Cognitive Decline (4 or more points on the MoCA-SA) and Baseline Sleep Characteristics in NSHAP Sleep Study (United States, 2010-2015).

Model[1]	Individual Sleep Parameters	Demographic Adjusted Models[2] (N=535)			Risk Factor Models[3] (N=402)		
		OR	95% CI	p-value	OR	95% CI	p-value
	Actigraph Measured Sleep Characteristics						
1	WASO[4]	1.43	1.04, 1.98	0.03	1.50	1.00, 2.24	0.05
2	Fragmentation[4]	1.30	0.96, 1.75	0.09	1.50	1.07, 2.10	0.02
3	Sleep Percent[4]	0.72	0.55, 0.94	0.02	0.63	0.44, 0.90	0.01
4	Wake Bouts[4]	1.00	0.77, 1.31	0.99	1.11	0.82, 1.49	0.50
5	Diurnal Phase[5]						
	8pm-1:59am	2.22	0.80, 6.18	0.13	3.03	0.82, 11.21	0.10
	2am-2:59am	1.00			1.00		
	3am-8:59am	1.13	0.62, 2.06	0.68	0.84	0.40, 1.76	0.64
	Total Sleep Time						
6	<6 hours	1.73	0.67, 4.50	0.26	3.41	1.19, 9.76	0.02
	6 - 6.99 hours	1.12	0.55, 2.27	0.75	1.47	0.66, 3.25	0.35
	7 - 7.99 hours	1.00			1.00		
	8 - 8.99 hours	1.14	0.47, 2.73	0.78	0.78	0.26, 2.35	0.66
	>= 9 hours	0.63	0.15, 2.60	0.52	0.50	0.11, 2.31	0.37
	P for trend	*0.21*			*<0.01*		
	Self-Reported Sleep Characteristics						
7	Self-Report Hours						
	<6 hours	1.54	0.68, 3.48	0.30	1.82	0.70, 4.73	0.22
	6 - 6.99 hours	0.98	0.31, 3.09	0.97	0.90	0.28, 2.95	0.86
	7 - 7.99 hours	1.00			1.00		
	8 - 8.99 hours	0.77	0.34, 1.71	0.52	0.76	0.28, 2.08	0.59
	>= 9 hours	0.79	0.30, 2.12	0.64	0.99	0.32, 3.04	0.98
	P for trend			*0.10*			*0.17*
8	Insomnia Symptoms[6]	1.08	0.93, 1.26	0.29	1.04	0.87, 1.24	0.69

Abbreviations: WASO, wake after sleep onset

[1]Model numbers indicate separate models.

[2]Logistic regression adjusted for: age, gender, race/ethnicity, education, and baseline MoCA-SA score

[3]Risk factor models additionally include frailty, depression, modified Charlson Comorbidity Index, sleep aids, antidepressants, alcohol use, daytime napping, physical activity, BMI, and sleep apnea

[4]Continuous sleep parameters are standardized

[5]Calculated from the average midpoint of sleep interval over three nights of actigraphy

[6]Range: 0-8 – a combined metric (0 = Never/rarely, 1 = Sometimes, 2 = Most of the time) from four questions: feeling rested in the morning, trouble falling asleep, trouble waking during the night and trouble waking too early. In the risk-adjusted models for the Troubled Sleep Scale, the depression scale, CES-D, does not contain the restless sleep item.

Table 1.5: Interaction between Gender and Sleep Characteristics on Cognitive Decline in NSHAP Sleep Study (United States, 2010-2015).

Model[1]	Individual Sleep Parameters	Demographic Adjusted Models[2] (N=535)		Risk Factor Models[3] (N=402)	
		OR	95% CI	OR	95% CI
1	WASO[4]				
	Men	1.85	1.25, 2.73	2.39	1.39, 4.12
	Women	1.20	0.76, 1.90	1.12	0.64, 1.95
	P value for interaction	0.15		0.06	
2	Fragmentation[4]				
	Men	1.83	1.27, 2.63	2.21	1.40, 3.48
	Women	0.95	0.62, 1.44	1.01	0.61, 1.67
	P value for interaction	0.02		0.03	
3	Sleep Percent[4]				
	Men	0.60	0.44, 0.84	0.49	0.31, 0.78
	Women	0.87	0.56, 1.35	0.79	0.45, 1.39
	P value for interaction	0.19		0.20	
4	Wake Bouts[4]				
	Men	1.34	0.98, 1.83	1.45	0.99, 1.32
	Women	0.67	0.44, 1.01	0.76	0.48, 1.21
	P value for interaction	<0.01		0.04	

Abbreviations: WASO, wake after sleep onset

[1]Model numbers indicate separate models. Each model includes parameters for main effects of gender and the sleep parameter and a gender by sleep parameter interaction term.

[2]Logistic regression models adjusted for: age, race/ethnicity, education, and baseline score on Montreal Cognitive Assessment – Survey Adapted

[3]Risk factor models additionally include frailty, depression, modified Charlson Comorbidity Index, sleep aids, antidepressants, alcohol use, daytime napping, physical activity, BMI, and sleep apnea

[4]Continuous sleep parameters are standardized

SUPPLEMENTAL MATERIAL

Both worse sleep and lower cognitive function were associated with no follow-up, due to death, ill health, or other reasons, and such selection might bias estimates of association. In a sensitivity analysis that assesses this potential selection bias, we used an adaptation of Heckman's two stage selection model. We generated an inverse Mills' ratio (IMR) using a probit model predicting the probability of inclusion in the sample based on age, gender, race/ethnicity, education, frailty, depression, and comorbidities and added this to the demographically adjusted logistic regression models.[72] We assessed the suitability of this method by first modeling our binary outcome in OLS models, as in Heckman's original selection model, then in probit and logistic regression models. To assess if we have bias due to selection, we compared the primary estimate of association across models, and assessed if the coefficients for sleep parameters changed with the addition of the IMR. If they did, this would suggest significant selection bias. We also looked at the coefficient for the IMR itself, the significance of which indicates a significant selection effect (Supplemental Table 1).

Supplemental Table 1.1: Assessment of Selection for Models of Cognitive Decline (4 or more points on the MoCA-SA) and Baseline Sleep Characteristics in NSHAP Sleep Study (United States, 2010-2015).

Model[1]	Individual Sleep Parameters	Demographic Adjusted Models[2]			Adjusted for Selection[3]		
		OR	95% CI	p-value	OR	95% CI	p-value
	Actigraph Measured Sleep Characteristics						
1	WASO[4]	1.43	1.04, 1.98	0.03	1.35	0.96, 1.92	0.09
	Mills' Ratio[5]				0.73	0.08, 6.91	0.79
2	Fragmentation[4]	1.30	0.96, 1.75	0.09	1.28	0.93, 1.75	0.12
	Mills' Ratio				0.69	0.07, 6.51	0.75
3	Sleep Percent[4]	0.72	0.55, 0.94	0.02	0.74	0.56, 0.98	0.04
	Mills' Ratio				0.71	0.08, 6.61	0.76
4	Wake Bouts[4]	1.00	0.77, 1.31	0.99	0.97	0.73, 1.29	0.83
	Mills' Ratio				0.80	0.08, 7.56	0.85
5	Diurnal Phase[6]						
	8pm-1:59am	2.22	0.79, 6.23	0.13	2.46	0.86, 7.04	0.09
	2am-2:59am	1.00			1.00		
	3am-8:59am	1.13	0.62, 2.06	0.68	1.11	0.60, 2.04	0.74
	Mills' Ratio				0.93	0.10, 8.65	0.95
6	Total Sleep Time						
	<6 hours	1.55	0.60, 4.01	0.37	1.78	0.67, 4.72	0.24
	6 - 6.99 hours	1.00			1.00		
	7 - 7.99 hours	0.89	0.44, 1.81	0.75	0.89	0.43, 1.86	0.76
	8 - 8.99 hours	1.01	0.44, 2.33	0.97	0.88	0.38, 2.05	0.77
	>= 9 hours	0.56	0.14, 2.27	0.42	0.58	0.13, 2.46	0.46
	Mills' Ratio				0.64	0.07, 5.98	0.70
	Self-Reported Sleep Characteristics						
7	Self-Report Hours						
	<6 hours	1.57	0.52, 4.78	0.43	2.40	0.77, 7.50	0.13
	6 - 6.99 hours	1.00			1.00		
	7 - 7.99 hours	1.02	0.32, 3.24	0.97	1.37	0.42, 4.45	0.60
	8 - 8.99 hours	0.78	0.25, 2.48	0.68	1.09	0.33, 3.59	0.89
	>= 9 hours	0.81	0.22, 3.04	0.75	1.19	0.32, 4.38	0.80
	Mills' Ratio				0.65	0.07, 5.61	0.69
8	Insomnia Symptoms[7]	1.08	0.93, 1.26	0.30	1.04	0.90, 1.20	0.62
	Mills' Ratio				0.65	0.07, 5.58	0.69

Abbreviations: WASO, wake after sleep onset

[1]Model numbers indicate separate models.

[2]Logistic regression models adjusted for: age, gender, race/ethnicity, education, and baseline MoCA-SA score

Supplemental Table 1.1, continued: Assessment of Selection for Models of Cognitive Decline (4 or more points on the MoCA-SA) and Baseline Sleep Characteristics in NSHAP Sleep Study (United States, 2010-2015).

[3]Coefficients for sleep parameters and Mills' Ratio for selection in Stage 2 of Heckman's two stage selection model with outcome modeled as binary in logistic regression. Additionally adjusted for: age, gender, race/ethnicity, education, and baseline MoCA-SA score.
[4]Continuous sleep parameters are standardized
[5]Mills ratio is derived from a probit model that predicts the probability of being included in the outcome based on age, gender, race/ethnicity, education, frailty, depression, and Charlson Comorbidity Index.
[6]Calculated form the average midpoint of sleep interval over three nights of actigraphy
[7]Troubled Sleep Scale (range:0-8) is a combined metric (0 = Never/rarely, 1 = Sometimes, 2 = Most of the time) from four questions: feeling rested in the morning, trouble falling asleep, trouble waking during the night and trouble waking too early. In the risk-adjusted models for the Troubled Sleep Scale, the depression scale, CES-D, does not contain the restless sleep item.

Supplemental Table 1.2: Sensitivity: Cognitive Decline of 3 or more points on the MoCA-SA and Baseline Sleep Characteristics in NSHAP Sleep Study (United States, 2010-2015).

Model[1]	Individual Sleep Parameters	Demographic Adjusted Models[2] (N=535)		
		OR	95% CI	p-value
		Actigraph Measured Sleep Characteristics		
1	WASO[3]	1.30	1.11, 1.33	0.08
2	Fragmentation[3]	1.25	0.96, 1.64	0.10
3	Sleep Percent[3]	0.80	0.62, 1.04	0.10
4	Wake Bouts[3]	1.05	0.83, 1.33	0.68
5	Diurnal Phase[4]			
	8pm-1:59am	2.16	0.78, 5.99	0.14
	2am-2:59am	1.00		
	3am-8:59am	1.06	0.63, 1.79	0.83
6	Total Sleep Time			
	<6 hours	1.35	0.57, 3.24	0.50
	6 - 6.99 hours	1.26	0.69, 2.29	0.46
	7 - 7.99 hours	1.00		
	8 - 8.99 hours	1.03	0.46, 2.30	0.94
	>= 9 hours	0.80	0.28, 2.31	0.69
	P for trend	0.43		
		Self-Reported Sleep Characteristics		
7	Self-Report Hours			
	<6 hours	1.78	0.87, 3.65	0.12
	6 - 6.99 hours	1.05	0.38, 2.89	0.92
	7 - 7.99 hours	1.00		
	8 - 8.99 hours	0.76	0.37, 1.53	0.44
	>= 9 hours	1.06	0.44, 2.56	0.90
	P for trend	0.08		
8	Insomnia Symptoms[5]	1.11	0.97, 1.26	0.13

Abbreviations: WASO, wake after sleep onset

[1]Model numbers indicate separate models.

[2]Logistic regression models adjusted for: age, gender, race/ethnicity, education, and baseline MoCA-SA score

[3]Continuous sleep parameters are standardized

[4]Calculated from the average midpoint of sleep interval over three nights of actigraphy

[5]Troubled Sleep Scale (range:0-8) is a combined metric (0 = Never/rarely, 1 = Sometimes, 2 = Most of the time) from four questions: feeling rested in the morning, trouble falling asleep, trouble waking during the night and trouble waking too early. In the risk-adjusted models for the Troubled Sleep Scale, the depression scale, CES-D, does not contain the restless sleep item.

Assessment of Previous Diagnoiss of Alzheimer's Disease and Dementia

Previous diagnoiss of Alzheimer's disease and dementia were assessed at baseline by asking participants:

"1. HAS A DOCTOR EVER TOLD YOU THAT YOU HAVE Alzheimer's disease?"

And

"2. IF NO TO QUESTION 2: HAS A DOCTOR EVER TOLD YOU THAT YOU HAVE dementia (including vascular dementia, mixed dementia, or Mild Cognitive Impairment)?"

Among sleep substudy participants, at baseline 5 answered yes to Alzheimer's and 9 to dementia. Excluding these individuals (n=14) from the models does not substantively change the estimates of association between the sleep parameters and concurrent or 5-year cognition.

Supplemental Table 1.3: Associations between Baseline Sleep Characteristics and Baseline MoCA-SA and between Baseline Sleep Characteristics and 5-year Cognitive Decline in the NSHAP Sleep Study (United States, 2010-2015), restricting to those without baseline dementia or Alzheimer's Disease.

Model[1]	Individual Sleep Parameters	OLS Cross-Sectional Models[2] (N=718)			Logistic 5-Year Follow-up[3] Models[2](N=468)		
		OR	95% CI	p-value	OR	95% CI	p-value
	Actigraph Measured Sleep Characteristics						
1	WASO[4]	-0.55	-0.81, -0.29	<0.01	1.44	1.04, 1.99	0.03
2	Fragmentation[4]	-0.47	-0.71, -0.23	<0.01	1.28	0.95, 1.73	0.11
3	Sleep Percent[4]	0.42	0.18. 0.67	<0.01	0.81	0.54, 0.94	0.02
4	Wake Bouts[4]	-0.34	-0.58, -0.10	<0.01	1.00	0.77, 1.31	0.98
5	Diurnal Phase[5]						
	8pm-1:59am	0.04	-0.62, 0.70	0.91	2.12	0.74, 6.03	0.16
	2am-2:59am	1.00			1.00		
	3am-8:59am	-0.03	-0.57, 0.52	0.93	1.11	0.61, 2.04	0.73
6	Total Sleep Time						
	<6 hours	0.04	-0.74, 0.82	0.92	1.89	0.72, 4.97	0.20
	6 - 6.99 hours	-0.08	-0.66, 0.50	0.80	0.20	0.59, 2.46	0.62
	7 - 7.99 hours	1.00			1.00		
	8 - 8.99 hours	-0.09	-0.81, 0.62	0.80	1.22	0.50, 2.99	0.66
	>= 9 hours	-0.63	-1.66, 0.39	0.22	0.67	0.16, 2.82	0.56
	P for trend	0.58			0.18		
	Self-Reported Sleep Characteristics						
7	Self-Report Hours						
	<6 hours	-0.74	-1.40, -0.09	0.03	1.51	0.66, 3.42	0.33
	6 - 6.99 hours	-0.51	-1.42, 0.40	0.28	0.99	0.31, 3.12	0.99
	7 - 7.99 hours	1.00			1.00		
	8 - 8.99 hours	-0.12	-0.74, 0.50	0.70	0.76	0.34, 1.70	0.51
	>= 9 hours	-0.660	-1.42, 0.22	0.15	0.21	0.26, 2.01	0.53
	P for trend			0.34			0.08
8	Insomnia Symptoms[6]	-0.00	-0.11, 0.11	0.98	1.08	0.93, 1.26	0.32

Abbreviations: WASO, wake after sleep onset

[1]Models include age, gender, race/ethnicity, and education. Baseline cognitive score is also included in the 5-year follow-up models; Model numbers indicate separate models.

[2]Outcome is baseline cognitive score

[3]Outcome is indicator of declining 4+ points over the 5-year period

[4]Continuous sleep parameters are standardized

[5]Calculated from the average midpoint of sleep interval over three nights of actigraphy

Supplemental Table 1.3, continued: Associations between Baseline Sleep Characteristics and Baseline MoCA-SA and between Baseline Sleep Characteristics and 5-year Cognitive Decline in the NSHAP Sleep Study (United States, 2010-2015), restricting to those without baseline dementia or Alzheimer's Disease.

[6]Troubled Sleep Scale (range:0-8) is a combined metric (0 = Never/rarely, 1 = Sometimes, 2 = Most of the time) from four questions: feeling rested in the morning, trouble falling asleep, trouble waking during the night and trouble waking too early. In the risk-adjusted models for the Troubled Sleep Scale, the depression scale, CES-D, does not contain the restless sleep item.

Supplemental Table 1.4: Sensitivity: Associations between Baseline Sleep Characteristics and Baseline MoCA-SA in the NSHAP Sleep Study (United States, 2010-2015), Risk Factor Models Adjusted for Apnea

Model[1]	Individual Sleep Parameters	Risk Factor Models[2] (N=404)		
		Coef.	95% CI	p-value
		Actigraph Measured Sleep Characteristics		
1	WASO[3]	-0.76	-1.11, -0.41	<0.01
2	Fragmentation[3]	-0.51	-0.85, -0.18	<0.01
3	Sleep Percent[3]	0.46	0.11, 0.81	0.01
4	Wake Bouts[3]	-0.40	-0.73, -0.08	0.02
5	Diurnal Phase[4]			
	8pm-1:59am	0.53	-0.29, 1.35	0.20
	2am-2:59am	1.00		
	3am-8:59am	0.36	-0.35, 1.08	0.32
6	Total Sleep Time			
	<6 hours	0.75	-0.22, 1.72	0.13
	6 - 6.99 hours	0.02	-0.73, 0.77	0.96
	7 - 7.99 hours	1.00		
	8 - 8.99 hours	-0.29	-1.08, 0.50	0.48
	>= 9 hours	-0.45	-1.60, 0.71	0.45
	P for trend	0.04		
		Self-Reported Sleep Characteristics		
7	Self-Report Hours			
	<6 hours	-0.52	-1.47, 0.42	0.28
	6 - 6.99 hours	-0.33	-1.57, 0.90	0.59
	7 - 7.99 hours	1.00		
	8 - 8.99 hours	0.08	-0.65, 0.80	0.84
	>= 9 hours	-0.21	-1.09, 0.67	0.63
	P for trend	0.35		
8	Insomnia Symptoms[5]	0.00	-0.14, 0.14	1.00

Abbreviations: WASO, wake after sleep onset

[1]Model numbers indicate separate models

[2]Risk factor models additionally include frailty, depression, modified Charlson Comorbidity Index, sleep aids, antidepressants, alcohol use, daytime napping, physical activity, BMI, and follow-up apnea indicator

[3]Continuous sleep parameters are standardized

[4]Calculated from the average midpoint of sleep interval over three nights of actigraphy

[5]Troubled Sleep Scale (range:0-8) is a combined metric (0 = Never/rarely, 1 = Sometimes, 2 = Most of the time) from four questions: feeling rested in the morning, trouble falling asleep, trouble waking during the night and trouble waking too early. In the risk-adjusted models for the Troubled Sleep Scale, the depression scale, CES-D, does not contain the restless sleep item.

Supplemental Table 1.5: Associations between Trouble Waking from Insomnia Symptom Scale and Baseline MoCA-SA and between Trouble Waking and 5-year Cognitive Decline in the NSHAP Sleep Study (United States, 2010-2015).

Model[1]	Sleep Parameter	OLS Cross-Sectional Models[2] (N=642)			Logistic 5-Year Follow-up Models[3] (N=468)		
		Coef.	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
	Trouble Waking[4]	0.03	-0.32, 0.37	0.88	1.26	0.82, 1.93	0.27

1Models include age, gender, race/ethnicity, and education. Baseline cognitive score is also included in the 5-year follow-up models
2Outcome is baseline cognitive score
3Outcome is indicator of declining 4+ points over the 5-year period
4Item in insomnia symptom scale: "How often do you have trouble with waking up during the night?" Responses are coded as: 0 = Never/rarely, 1 = Sometimes, 2 = Most of the time

TEMPORAL VARIATION IN THE STRENGTH OF ASSOCIATION BETWEEN *APOE* E4 AND COGNITIVE DECLINE

INTRODUCTION

The Apolipoprotein (*APOE*) ε4 allele is a well-established genetic risk factor for Alzheimer's disease (AD).[20–22] Among those with AD, possession of an ε4 allele (carriers) have earlier age of onset, more rapid cognitive decline, and higher levels of impairment.[90–92] Although carriers are at higher risk for AD diagnosis, there is less evidence as to whether the ε4 allele is associated with cognitive decline prior to, or in the absence of, an AD diagnosis. Possession of at least one ε4 allele has been found to be associated with cognitive decline in many studies, but the magnitude of the association between the e4 allele and cognitive decline varies substantially between studies.[24–26]

This heterogeneity among studies could be the result of differences in study design, such as the length of observation or the type of cognitive assessment, or it could be due to the effect of the ε4 allele actually differing across population groups. This could be due, for example, to differences in study populations in terms of age composition, genetic ancestry of the cohort, or socioeconomic status.

Directly testing potential effect modifiers within a single study would help clarify whether heterogeneity between studies is due to study design differences or to effect modification of the ε4 allele by population characteristics. There have been a few such investigations, and they have focused on two types of potential effect modifiers, environmental factors measured at the time that cognitive function is being assessed, such as physical activity level, and educational attainment.

Gene by environment interaction studies considering educational attainment yield mixed results in assessing modification of the effect of the ε4 allele on cognitive decline. Shandlen, et al observed that among *APOE* ε4 carriers, individuals with a higher education were more likely to

have a smaller decrease in cognitive function at 6-years follow-up compared to those with lower education.[93] However, other studies have found that higher education led to steeper decline in cognitive function compared to lower education among *APOE* ε4 carriers.[94,95] One possibility for this counterintuitive result is due to higher baseline cognitive function of those with higher education, irrespective of *APOE* status, giving those individuals more scope for cognitive decline. Another model of why one might observe a gene-by-environment interaction (GxE) where the genetic effect is stronger in the more advantaged group posits that adverse environmental exposures overpower and mask weaker genetic effects while average or more salubrious environments reveal more fully the genetic contribution to the trait or outcome.[96] Such a relationship has also been observed in studies with non-cognitive endpoints.[97,98]

Initially, examinations of GxE interactions on cognitive decline focused on biological risk factors for cardio-vascular disease (CVD), in particular. Findings have shown risk factors for CVD such as hypertension and diabetes are more strongly linked to cognitive outcomes among those with an ε4 allele compared to those without.[99–101] More recently, examinations of whether the penetrance of the *APOE* ε4 allele varies by environmental factors have considered temporally proximate factors. Evidence has been mixed. Studies have found that high stress levels and high neighborhood psychosocial hazards interact with the ε4 allele to produce worse cognitive function[102,103]. In contrast, one study found that those living in neighborhoods with *low* levels of neighborhood social disorder showed a stronger association between the ε4 allele and cognitive decline, compared to those in high social disorder neighborhoods with an ε4 allele.[96] Still, a number of studies have also presented null results with regard to interactions between measures of environment and the *APOE* ε4 allele, including for employment grade,[35] physical activity,[104] and engagement in social and leisure activities.[105] This focus on mid- to late-life behaviors and

circumstances as potential effect modifiers is likely due to the relative accessibility of data about the proximal contemporaneous environment when enrolling study participants in later life.

A vast and growing literature has demonstrated that the early-life environment is associated with a variety of late-life health outcomes. At the individual level, Barker's fetal origins hypothesis posits that the nutritional environment that a fetus experiences in utero can alter the metabolic characters that the offspring will experience during the life course, influencing their risk for diverse health outcomes.[106,107] In many studies, birth-year cohort has been used as a proxy for cohort-wide exposures for both short-term events that may affect a developmental period, such as the flu pandemic or smallpox outbreak years, or natural disasters and economic crises; and also for changing environments over time with respect to factors such as educational distribution and access or resources.[40,42–44,46]

The early-life environment has been shown to affect cognitive aging. Specifically, early-life socioeconomic level at home and in the community,[28–30] cognitively stimulating activity in early childhood,[31,32] and adversity in childhood[33,47] have been associated with late-life cognitive variation. To represent the early-life environment, Case and Paxson used census region infant mortality as a measure of burden of disease early in life and observed that high mortality rates were associated with lower performance on cognitive tests in older age.[41] Doblhammer, et al looked at economic recessions by country in Europe and found that birth-year cohorts born during recessions had lower average cognitive function in older age.[42] Broadly, age-adjusted average cognition and incidence of neurodegenerative diseases favor more recent birth cohorts.[43–46] While some of this improvement has been attributed to increasing access to and quality of education, investigators have also proposed that some of this improvement may be due better early-life circumstances including the economic, social, and disease environments.

The potential for birth-year cohort to explain some of the heterogeneity across studies in the magnitude of effect of the *APOE* ε4 allele on cognitive decline has not been explicitly explored. We hypothesize that being born into a more resource rich environment, operationalized via postwar vs. prewar birth-year cohort, blunts the effect of the *APOE* ε4 allele on cognitive function late in life and on cognitive decline. Specifically, we ask whether there is a gene by birth-year cohort interaction on the effect of the *APOE* ε4 allele on cognitive decline among adults aged 50 to 75 years. We further consider whether differences in allele penetrance by birth-year cohort can be attributed to changes in educational attainment between cohorts.

DATA AND METHOD

This analysis uses the Health and Retirement Study (HRS). The HRS is an ongoing nationally representative longitudinal study of U.S. adults over age 50. Respondents are re-interviewed every two years and provide extensive information on social and economic factors as well as health. We use the Rand HRS Longitudinal File 2016 (v1), which is a cleaned version of the core interviews merged across all HRS waves.

Cohort

HRS was initiated in 1992 when individuals born between 1931 and 1941 were enrolled (HRS cohort). Since then, five additional birth-year cohorts have been enrolled: Study of Assets and Health Dynamic (AHEAD, b. 1923 or earlier), Children of Depression (CODA, b. 1924-1930), War Baby (WB, b. 1942-1947), Early Boomers (EBB, b. 1948-1953), and Mid Boomers (MBB, b. 1954-1959). In this analysis, we combine these six groups into two birth-year cohorts – those born before the start of World War II (AHEAD, CODA, and HRS cohorts) and those born after (WB, EBB, and MBB). To compare cognitive change for these two birth-year cohorts for

individuals of the same age, we limit our analysis to interviews given between the ages of 50 to 75 (see Figure 1).

Genetic Data

HRS collected saliva samples from different participants in 2006, 2008, and 2010. Combining the three collection periods, saliva samples were collected from over 80% of the surviving participants. Of the total 37,939 HRS participants, 15,567 individuals have genotyped data. In 2006, saliva was collected via buccal swabs and in 2008 and 2010 with saliva, using the Oragene DNA self-collection kit. Genotyping used the Illumina's Human Omni2.5 Quad Bead Chip and imputed using the 1000G phase 1 reference panel. Genetic information was filed with the Database for Genotypes and Phenotypes (dbGap), from which we accessed it.

The two single nucleotide polymorphisms (SNPs), rs429380 and rs7412, define the three *APOE* alleles (ε2, ε3, and ε4)[27]. The most common allele is *APOE* ε3 whereas *APOE ε4* is the allele associated with AD pathology. There is some evidence that the *APOE* ε2 allele is protective against AD pathology. In this analysis we identify individuals with one or two ε4 alleles as having higher risk for cognitive decline, excepting those with both an ε4 *and* an ε2 allele (2.4%) whom we drop from analysis given the protective nature of the ε2 allele. Supplemental Table 1 shows the identification of the *APOE* haplotypes in the HRS genetic data. All models account for population stratification with the first two eigenvectors from the principal components (PC) analysis that was performed by HRS.

Cognition

Beginning in 1996, cognitive function was measured at each wave using a 35-point scale derived from the Telephone Interview for Cognitive Status (TICS), the HRS TICS-m. The original TICS, based on the Mini-Mental State Examination (MMSE), assesses different

cognitive domains: memory (immediate and delayed 10-word recall), attention and processing speed (backwards counting from 20), working memory (serial 7s subtraction), language (object naming), and orientation (recall of day, month, year, day of week, and president and vice-president). Characterization of cognition using the HRS data has been consistent with other comparable national surveys, although there are few large, nationally-representative longitudinal studies with genotype data[108]. The HRS cognitive data have been used to describe both cognitive function between groups and change in cognition over time in a number of studies[109–111].

Other Covariates

Because we are considering whether early-life environment modifies the penetrance of genetic risk for cognitive decline, we only control for genetic ancestry and sex. There is variation in the distribution of the ε4 risk allele by genetic ancestry and as such, we restrict our sample to self-identified white as there is insufficient power to detect birth-year cohort difference in cognitive decline due to genetic risk in the other racial subpopulations. Within self-identified whites, we adjust for genetic ancestry using the first two PCs, which has been shown to be sufficient.

Analytic Sample

We limited our analytic sample to individuals who had a birthdate within the birth-year cohorts of interest, self-identified whites, those who had genetic data including information on the two *APOE* SNPs of interest and the first two PCs, and who had outcome data (cognitive score). At the level of observation (each unique encounter), we limited the sample to the observations for each respondent when they were within our pre-specified age range (50 to 75), and we excluded individuals who reported incident dementia beginning with the interview when

they made that report. With these inclusion criteria, our analytic sample consisted of 9,836 individuals contributing 33,912 observations.

Statistical Analysis

We examine both level of cognitive function and change in cognitive function over time by cohort and ε4 status, employing mixed-effects models. In this approach, the mean rate of change and the age-centered level of cognition is modeled, while individuals are allowed to have random variation from both the age-centered level of cognition (can be higher or lower than the mean) and from the rate of change (can be faster or slower).

We first fit a main effects model with covariates for age (rate of decline), birth-year cohort (prewar vs. postwar), and *APOE* ε4 allele status (any ε4 allele vs. none). We then fit a model with three two-way interactions, so that each main effect interacts with the other two main effects. We finally fit a model with all two-way interactions and a three-way interaction to assess whether the effect of the *APOE* ε4 allele on cognitive decline differed by birth-year cohort. Control variables are sex and a vector of coefficients for the first two principal components to adjust for genetic ancestry.

We subsequently add education to each model in order to assess whether education explains any difference in average cognitive function or change in cognitive function by birth-year cohort and ε4 status. We model education as a continuous variable representing years of education completed at the individual level.

In our supplemental materials, we additionally present change-point models of decline. Change point models allow the rate of decline to change at a pre-specified point; in our model, this point is an age. We considered twenty-four change point models, one for each age in the age range, as well as a model with a quadratic term for age. We then compared all models on the

basis of log likelihood, Akaike's information criterion, and Bayesian information criterion. This led us to choose a change point model with 67 as the point of inflection. While some previous analyses of cognitive decline have found that a change-point model fits decline trajectories over time better than a model in which age is treated as a linear effect[112,113], there are relatively few sequential observations here for the postwar birth-year cohort to estimate change in cognitive function after age 67, which is a limitation for the interaction models which are our primary interest.

RESULTS

Characteristics of the 9,836 individuals in the analytic sample are presented in Table 1. The prewar birth-year cohort represents 61% of the sample. Consistent with other population-based studies, about one fourth of the both birth-year cohorts has at least one *APOE* ε4 allele. The proportion of those with an ε4 allele is not different between birth-year cohorts. Average years of education completed is higher in the postwar group (mean=13.4, sd=3.0) than in the prewar group (mean=12.6, sd=3.0).

Cognitive Level and Cognitive Change

The three mixed-effects models that were fit to the data to examine average cognitive function at age 60 and cognitive change over time as a function of risk allele status and birth-year cohort are presented in Table 2. Model 1 includes only main effects for the included terms, Model 2 includes all two-way interactions for the terms of interest (age, allele status, and birth-year cohort), and Model 3 additionally includes the three-way interaction. All models are additionally adjusted for sex and the first two principal components to adjust for genetic ancestry (not shown).

In Model 1, having an ε4 allele, being in the postwar birth-year cohort, and age are all negatively associated with cognitive function at age 60 as measured by the TICS scale. At age 60, the average TICS score of those with an ε4 allele is 0.28 lower than those without the risk allele. Those in the postwar birth-year cohort, on average, have a 0.84 lower TICS score than those in the prewar birth-year cohort, and each additional year of age is associated with a 0.15 point decrease on the TICS measure. Model 2 includes two-way interactions for all of the terms. The rate of decline is slower in the postwar birth-year cohort (β = 0.05, 95% CI: 0.03, 0.06) and faster for those with an *APOE* ε4 allele (β = -0.04, 95% CI: -0.06, -0.03). For those with an *APOE* ε4 risk allele, there is no evidence of a difference in average cognitive function at age 60 in the prewar versus the postwar birth-year cohort (β = -0.16, 95% CI=-0.53, 0.22).

Model 3 includes a three-way interaction with age, *APOE* ε4 status, and birth-year cohort. This term estimates the difference in the rate of cognitive decline by *APOE* ε4 status and birth-year cohort. The interaction term is positive and significant (β = 0.07, 95% CI: 0.04, 0.11), indicating that those in the postwar birth-year cohort experience a weaker effect than the prewar birth-year cohort in terms of the risk of cognitive decline associated with possessing an ε4 risk allele.

Figure 2 is a visual representation of the cognitive decline of the four groups defined by allele status and birth-year cohort. The figure shows decline due to age in the postwar birth-year cohort is very similar whether in ε4 positive group (β = -0.11, 95% CI: -0.13, -0.08) or in the ε4 negative group (β = -0.12, 95% CI: -0.13, -0.11), whereas in the prewar birth-year cohort, those with an ε4 allele have a much greater rate of decline over age (β = -0.21, 95% CI: -0.23, -0.20) compared to those without an ε4 allele (β = -0.15, -0.16, .0-14).

Table 3 shows the progression of the mixed-effect model building, with education added to each model. In each model, education is similarly associated with better average cognitive function. In Model E3, the difference in the rate of cognitive decline by *APOE* ε4 status and birth-year cohort is not substantively different than the model without education (β=0.06, 95% CI: 0.03, 0.10).

DISCUSSION

In a nationally representative longitudinal cohort of older adults, we have found that the relationship between the *APOE* ε4 risk allele and cognitive decline over age varies by birth-year cohort. Specifically, in the prewar birth-year cohort, the rate of decline for those that have an ε4 allele was 40% worse than for those that do not have an ε4 allele whereas in the postwar birth-year cohort, the rate of decline did not differ by risk allele status. When we included education in our mixed-effects models, the magnitude of association between the ε4 allele and cognitive decline was not attenuated, nor was the difference in the impact of the allele between birth-year cohorts lessened. One unexpected observation was that the beta coefficient of -0.80 for birth-year cohort indicated that the postwar birth-year cohort had a lower average cognitive function at age 60 compared to the prewar birth-year cohort, despite higher average levels of education in the postwar birth-year cohort. However, we also observe that the prewar birth-year cohort has steeper age-related decline leading to similar average cognitive function between birth-year cohorts by age 75.

While no previous studies have considered differences in the association between *APOE* and cognitive decline across birth-year cohorts, there are three literatures in which we can situate the current paper. First, a handful of studies have looked at variation in genetic penetrance by birth-year cohort. Conley et al, have demonstrated variation in genetic penetrance of polygenic

scores by birth-year cohort on education, body mass index (BMI), height, and heart disease in HRS.[54] They find that genetic effects for height and BMI increase over later born cohorts. However, and perhaps consistent with our finding, they observe that the genotypic effect on education decreases with later born cohorts. Our study differs in that we look at late life cognitive decline as an outcome and consider the *APOE* gene, as opposed to a polygenic score. Other gene by birth-year cohort studies have observed variation in genetic penetrance on BMI and smoking.[51,53,114] Second, some studies have sought to assess whether there is variation in the relationship between the *APOE* ε4 allele and late life cognitive outcomes by individual (as opposed to cohort-wide) markers of early-life environment. Many of these studies have used head circumference as a marker of prenatal and/or early-life circumstances noting that during gestation and in the first year of life, the brain grows to 75% of adult size, with the additional 25% growth happening in the next few years up to about age 7.[115] The deleterious effects of the *APOE* ε4 allele on cognitive decline were less evident in those with a larger head circumference.[115–118] These papers, in particular, speak to the idea that conditions that could influence very early-life environment, such as nutritional status, could be influential in protecting against the risk of possessing an *APOE* ε4 allele. Two additional studies found that childhood SES modified the relationship between the *APOE* ε4 allele and risk of dementia in that higher childhood SES was protective against the risk whereas lower SES intensified the risk.[119,120] The third set of studies are those which have considered changes in cognitive outcomes by birth-year cohort. The literature here has been mixed, with some studies finding no differences in cognitive decline between birth-year cohorts[121,122], some finding that later born cohorts have less steep decline[44,123], and one finding that the later born cohort had a steeper decline.[46] The studies finding no difference between birth-year cohorts were distinct from this analysis in notable ways:

first, one study was conducted in Sweden, which may have seen different social changes over the years under analyses and second, both studies were comparing birth-year cohorts that were older than the younger cohort in our analysis. The Swedish study compared birth years of 1900-1925 to 1926-1948 and the other, using data from the Long Beach Longitudinal Study, compared 1893-1923 to 1908 to 1940. However, one study that did find differences in decline favoring the later born cohort also had older cohorts, Gerstorf, et al. used the Seattle Longitudinal Study to compare those born 1886-1913 to 1914-1948. The other cohort observing a favorable decline for the later born cohort used data from the General Social Survey and had 1940 as a birth-year divider between cohorts, comparable to our study. The study finding a steeper decline had Swedish population samples born in 1901, 1906 and 1930 and suggest that selective survival may contribute to their surprising findings.[46] In our models, the two-way interaction between age and birth-year cohort does indicate that the postwar birth-year cohort experienced less rapid decline, compared to the prewar birth-year cohort.

Why might we observe birth-year cohort differences in the effect of *APOE* ε4 in this particular population? The United States saw large scale shifts in infant mortality, nutritional environment, the expansion of free and compulsory education, and medical advancements in the 20th century, all of which have been associated with positive later life health outcomes and longevity. The prewar versus postwar period marked a historical moment for many of these shifts in the United States, with advances in technology, access to education and the work force for many women, and more widespread socioeconomic wellbeing for large swaths of the population. In the context of cognitive decline, it is possible that as the early-life environment became more salubrious, capacity for resistance to genetically associated cognitive decline increased.

One possible explanation for the development of such resistance which we've explored could be the increase in educational access and attainment between birth-year cohorts. The mechanism of this possible explanation is complicated: it is influenced by the socioeconomic environment in childhood and then predicts the socioeconomic status of adulthood. Further, being in school during formative years could have a direct effect on cognitive aging by contributing to cognitive development during a sensitive period of growth,[124] however some studies have found that only early education confers such direct protection, not the number of subsequent years.[125,126] Overall educational attainment could also be taken to indirectly reflect other environmental heterogeneities such as early-life circumstances and familial socioeconomic background; period effects to do with quality of educational systems or changing accessibility of careers by educational attainments over time;[127] or career trajectories and later life socioeconomic position.[124] However, despite the change in educational attainment observed in the prewar versus postwar birth-year cohorts, where nearly 10% more of the postwar birth-year cohort earned a college degree compared to the prewar birth-year cohort, we did not observe that this change explained evidence of diminished penetrance of the *APOE* ε4 allele on cognitive decline in the postwar birth-year cohort.

There are many strengths to the present analysis. We use a nationally representative and large population-based cohort that spans a wide range of birth years and includes longitudinal follow-up time with multiple observations for each subject. This allows us to observe cognitive trajectories over many years and to situate those trajectories in the national context, which makes the birth-year cohort comparison well-suited to this particular data set. Adherence to genetic testing in the HRS cohort has been very high, limiting concern about bias due to sample selection for genetic data collection participation. The cognitive measure in HRS is a validated measure of

global cognition which has been used to report age-related changes in cognitive performs what are similar to other cognitive measures.

There are also limitations to this analysis that must be mentioned. First, we have much more limited data in terms of longitudinal follow-up time for the later-born cohort. Because of this we had to limit our sample to the age range of 50-75 to ensure sufficient overlap between the birth-year cohorts so they could be compared at the same age ranges. This prevents us from observing cognitive decline that happens after age 75, which is a period when the *APOE* ε4 allele has been shown to have stronger effects, compared to early older age (before age 60), and when we generally see greater cognitive decline. Second, although there was high adherence to the genetic testing, the testing took place in 2006 – more than a decade after initial enrollment in the HRS had begun. It is very likely that there was a survival bias in terms of who survived to be able to participate in the genetic testing which was most influential on the prewar birth-year cohort. Finally, in this analysis, we consider global cognitive decline, which in some studies has been shown to be less sensitive to the presence of the ε4 allele than specific cognitive domains, such as memory, which may be more likely to be affected by genetic predisposition to neurodegenerative pathology.

This analysis considers a previously unasked question of whether the genetic penetrance of the *APOE* ε4 allele with respect to cognitive decline has changed over time, specifically by birth-year cohort. We further inquire as to whether evidence of difference between birth-year cohorts could be due to changes in educational attainment, and we find that it is not. We find that the effect of the *APOE* ε4 allele is weaker for the more recent birth-year cohort.

ACKNOWLEDGEMENTS

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Figure 2.1: Age distribution of birth-year cohorts and area of overlap in the Health and Retirement study

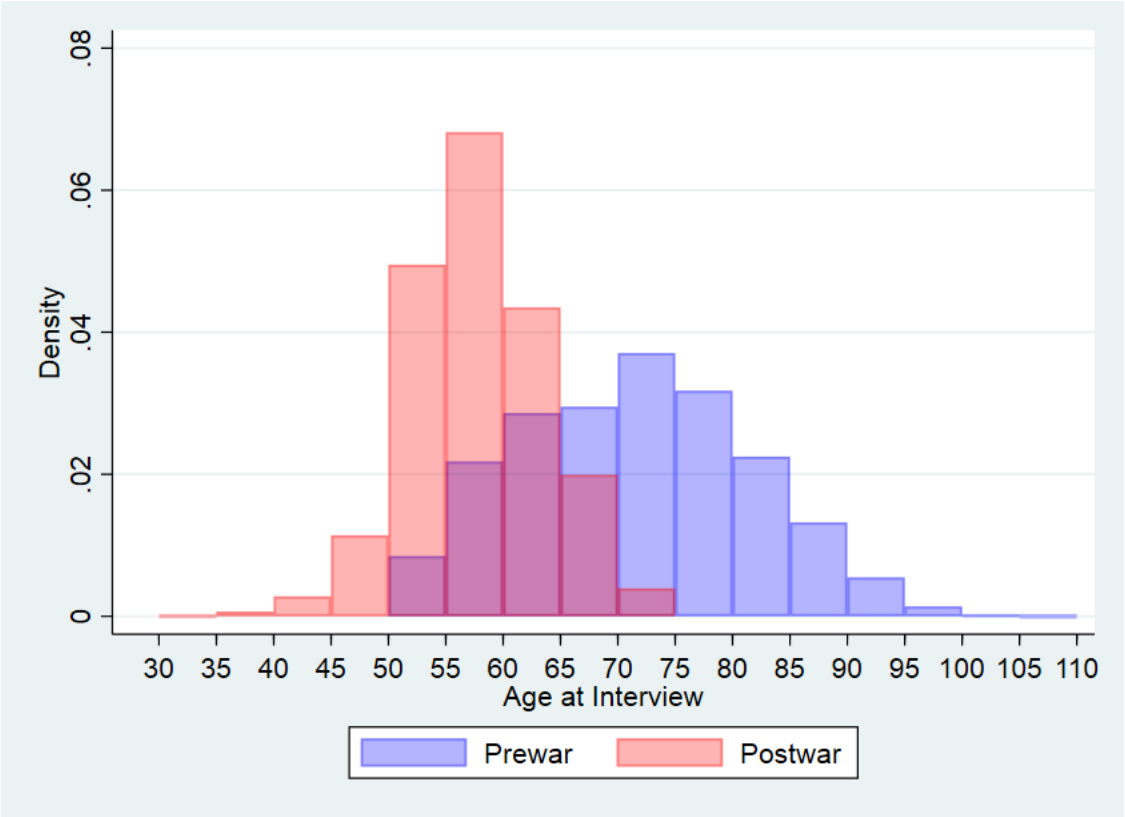

Table 2.1: Demographic characteristics of Health and Retirement Study analytic sample subjects by birth-year cohort (N=9,836)

	Prewar (b. 1894-1941) N=5,974	Postwar (b. 1942-1959) N=3,862
Age at first interview	63.38 (6.13)	53.27 (2.57)
Female	55.86%	55.18%
Any *APOE* ε4 allele	24.15%	23.77%
Deceased	23.67%	5.13%
Education		
Years (mean (sd))	12.57 (3.02)	13.35 (2.97)
Level		
<High School	19.05%	11.40%
GED/High School	39.37%	31.57%
Some College	20.61%	27.17%
College	20.97%	29.86%

*Analytic sample is limited to white-identified subjects who have genetic data, did not have a dementia diagnosis at baseline and who participated in the HRS at least once during ages 50-75.

Table 2.2: Mixed-effects linear models predicting cognitive function and decline on *APOE* allele status, birth-year cohort, and age in the Health and Retirement Study analytic sample (N=9,863), 1996-2014.

	Model 1			Model 2			Model 3		
	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
APOE	-0.28	[-0.44,-0.12]	<0.01	-0.07	[-0.30,0.16]	0.58	0.09	[-0.15,0.33]	0.46
Postwar	-0.84	[-1.00,-0.68]	<0.01	-0.80	[-0.98,-0.62]	<0.01	-0.80	[-0.98,-0.62]	<0.01
Age	-0.15	[-0.16,-0.15]	<0.01	-0.16	[-0.17,-0.15]	<0.01	-0.15	[-0.16,-0.14]	<0.01
*APOE**Postwar				-0.16	[-0.53,0.22]	0.42	-0.15	[-0.52,0.23]	0.44
Age*Postwar				0.05	[0.03,0.06]	<0.01	0.03	[0.01,0.05]	<0.01
Age**APOE*				-0.04	[-0.06,-0.03]	<0.01	-0.06	[-0.08,-0.04]	<0.01
Age**APOE**Postwar							0.07	[0.04,0.11]	<0.01
Constant	22.41	[22.05, 22.78]		22.46	[22.10, 22.83]		22.43	[22.06, 22.79]	

*Models are adjusted for sex and a vector of coefficients for the first two principal components. Age is centered at 60.

Figure 2.2: Estimated cognitive trajectories from mixed-effect models by birth-year cohort and *APOE* ε4 status over age in the Health and Retirements Study analytic sample

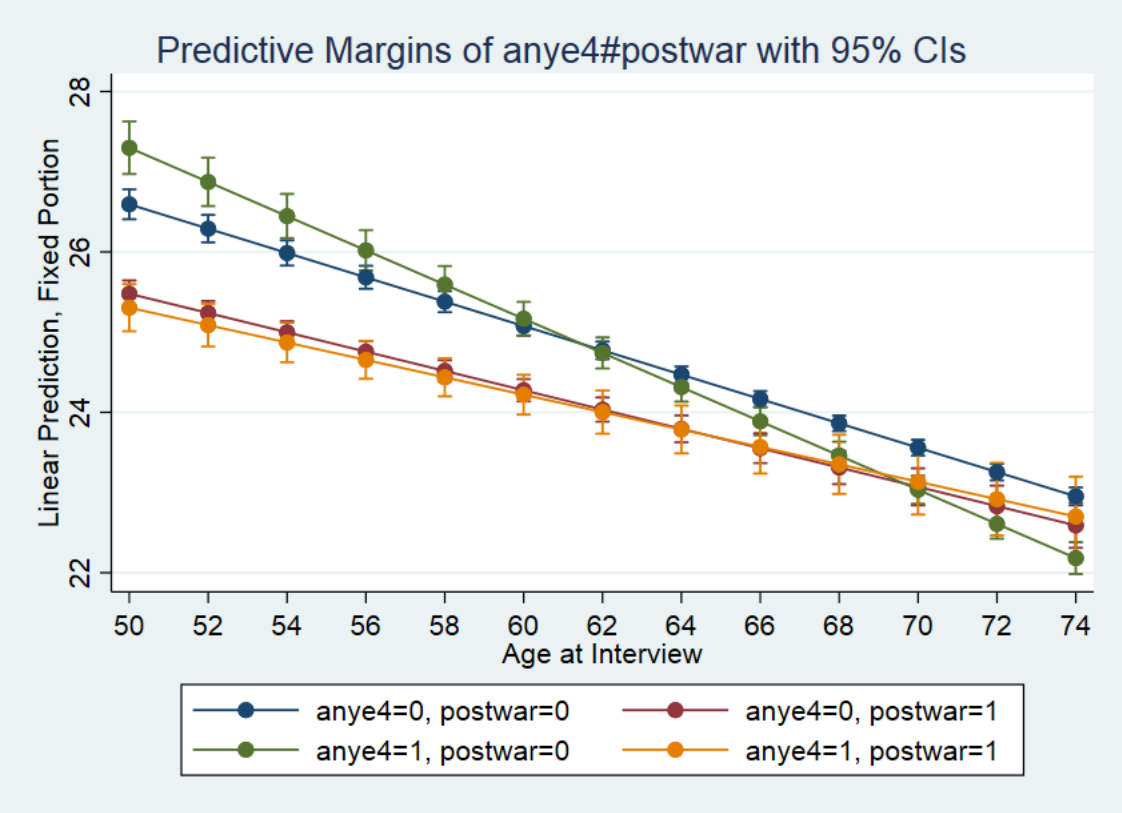

Table 2.3: Mixed-effects linear models predicting cognitive function and decline on *APOE* allele status, birth-year cohort, and age in the Health and Retirement Study analytic sample (N=9,863), and adjusting for level of education, 1996-2014,

	Model E1			Model E2			Model E3		
	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
APOE	-0.31	[-0.45,-0.16]	<0.01	-0.07	[-0.28,0.14]	0.52	0.07	[-0.16,0.29]	0.56
Postwar	-1.23	[-1.37,-1.08]	<0.01	-1.19	[-1.36,-1.03]	<0.01	-1.19	[-1.36,-1.02]	<0.01
Age	-0.15	[-0.15,-0.14]	<0.01	-0.15	[-0.16,-0.14]	<0.01	-0.15	[-0.16,-0.14]	<0.01
*APOE**Postwar				-0.18	[-0.52,0.17]	0.31	-0.19	[-0.53,0.16]	0.29
Age*Postwar				0.06	[0.04,0.07]	<0.01	0.04	[0.02,0.06]	<0.01
Age**APOE*				-0.04	[-0.06,-0.03]	<0.01	-0.06	[-0.08,-0.04]	<0.01
Age**APOE**Postwar							0.06	[0.03,0.10]	<0.01
Education	0.56	[0.53,0.58]	<0.01	0.56	[0.54,0.58]	<0.01	0.56	[0.54,0.58]	<0.01
Constant	15.43	[15.00, 15.86]		15.47	[15.04, 15.90]		15.45	[15.02, 15.88]	

*Models are adjusted for sex and a vector of coefficients for the first two principal components. Age is centered at 60.

Supplemental Table 2.1: *APOE* haplotype determination in the HRS Genetic Sample

	rs7412			
		CC	CT	TT
rs429380	TT	e3/e3	e2/e3	e2/e2
	N	9,247	1,866	106
	(%)	(60.33)	(12.17)	(0.69)
	CT	e3/e4	e1/e3 or e2/e4	e1/e2
	N	3,407	369	0
	(%)	(22.23)	(2.41)	(0)
	CC	e4/e4	e1/e4	e1/e1
	N	332	0	0
	(%)	(2.17)	(0)	(0)

Supplemental Table 2.2: Mixed-effects change-point models predicting cognitive function and decline on *APOE* allele status, birth-year cohort, and age in the Health and Retirement Study analytic sample (N=9,863), 1996-2014.

	Model 1 B (95% CI)	Model 2 B (95% CI)	Model 3 B (95% CI)
APOE	-0.28 (-0.44,-0.12)	-0.17 (-0.39,0.05)	-0.24 (-0.47,-0.01)
Postwar	-0.66 (-0.82,-0.50)	-0.66 (-0.89,-0.43)	-0.71 (-0.95,-0.47)
Decline up to age 67	-0.11 (-0.12,-0.10)	-0.10 (-0.12,-0.09)	-0.1 (-0.11,-0.08)
Decline after age 67	-0.23 (-0.24,-0.22)	-0.21 (-0.22,-0.19)	-0.21 (-0.23,-0.19)
*APOE**Postwar		-0.04 (-0.42,0.34)	0.15 (-0.34,0.65)
Decline up to age 67**APOE*		-0.01 (-0.03,0.01)	-0.04 (-0.07,-0.01)
Decline after age 67**APOE*		-0.09 (-0.13,-0.06)	-0.09 (-0.12,-0.05)
Decline up to age 67*Postwar		0.00 (-0.02,0.02)	-0.01 (-0.04,0.01)
Decline after age 67*Postwar		-0.04 (-0.17,0.09)	-0.11 (-0.25,0.04)
Decline up to age 67**APOE**Postwar			0.04 (-0.00,0.09)
Decline after age 67**APOE**Postwar			0.28 (-0.02,0.59)
Log Likelihood	-89253.81	-89231.29	-89226.73
Chi-sq (d.f.), and p-value for LR test		45.04 (5), p<0.01	9.12 (2), p=0.01

*Models are adjusted for sex and a vector of coefficients for the first two principal components. Age is centered at 60.

Supplemental Table 2.3: Mixed-effects change-point models predicting cognitive function and decline on *APOE* allele status, birth-year cohort, and age in the Health and Retirement analytic sample (N=9,863), and adjusting for education, 1996-2014.

	Model 1 B (95% CI)	Model 2 B (95% CI)	Model 3 B (95% CI)
APOE	-0.31 (-0.45,-0.17)	-0.2 (-0.40,-0.00)	-0.25 (-0.46,-0.04)
Postwar	-1.05 (-1.20,-0.90)	-1.01 (-1.22,-0.79)	-1.04 (-1.26,-0.81)
Decline up to age 67	-0.1 (-0.11,-0.09)	-0.1 (-0.11,-0.08)	-0.09 (-0.11,-0.08)
Decline after age 67	-0.23 (-0.24,-0.21)	-0.2 (-0.22,-0.19)	-0.2 (-0.22,-0.19)
*APOE**Postwar		-0.08 (-0.43,0.27)	0.03 (-0.43,0.49)
Decline up to age 67**APOE*		0 (-0.02,0.02)	0 (-0.03,0.02)
Decline after age 67**APOE*		-0.09 (-0.12,-0.06)	-0.09 (-0.12,-0.05)
Decline up to age 67*Postwar		-0.02 (-0.04,0.00)	-0.04 (-0.07,-0.01)
Decline after age 67*Postwar		-0.02 (-0.15,0.10)	-0.09 (-0.23,0.06)
Decline up to age 67**APOE**Postwar			0.03 (-0.01,0.07)
Decline after age 67**APOE**Postwar			0.28 (-0.02,0.58)
Education (years)	0.56 (0.53,0.58)	0.56 (0.54,0.58)	0.56 (0.54,0.58)
Log Likelihood	-88107.03	-88080.37	-88083.70
Chi-sq (d.f.), and p-value for LR test (compared to parallel model without education)	2135.14 (1), p<0.01	2134.31 (1), p<0.01	2136.91, p<0.01
Chi-sq (d.f.), and p-value for LR test (compared to previous model)		53.32 (7), p<0.01	6.67 (2), p=0.04

*Models are adjusted for sex and a vector of coefficients for the first two principal components. Age is centered at 60.

DO ADVERSE CHILDHOOD EXPERIENCES MODIFY THE EFFECT OF THE *APOE* E4 ALLELE ON COGNITIVE OUTCOMES AND POSTMORTEM NEUROPATHOLOGY?

INTRODUCTION

The primary mechanism by which the *APOE* ε4 allele, the major genetic risk factor for Alzheimer's disease (AD), is thought to negatively impact cognitive outcomes in older adults is via increased neuropathological burden.[128–130] Older adults with one or two *APOE* ε4 alleles have been shown to have higher levels of amyloid-beta (Aβ) and tau protein (tangles) and higher risk for cerebrovascular outcomes.[131–135] Lifestyle or environmental characteristics can modify the relationship between genetic risk for AD and cognitive decline via modification of the neuropathology outcomes themselves or via modification to resilience or susceptibility to these pathogenic risks.

Most evidence points to positive lifestyle and environmental factors being related to increased cognitive reserve (the capacity to cope with or compensate for pathology). Factors can include lifestyle characteristics which are measured contemporaneous to cognitive outcomes, such as larger social networks, but also include factors that originate early in life and span the life course, such as education and participation in cognitively stimulating activities throughout life. These factors are all associated with resistance to pathology associated with cognitive decline.[50,136,137] However, there is also evidence that early-life cognitive engagement may be related with lower levels of neuropathology later in life. Landau, et al found that participation in cognitively stimulating activity throughout life, but particularly in early and mid-life was protective against cortical Pittsburgh Compound B, a measure of β-amyloid deposition.[138] Evidence from the Nun Study shows that early-life linguistic ability (measured via idea density derived from autobiographies written by the nuns in their early twenties) among participants in the study was associated with pathology outcomes related to AD including neurofibrillary pathology and meeting pathologic criteria for AD.[49,139]

In contrast, adverse early-life circumstances have been associated not only with lower cognitive function and more rapid cognitive decline but also with faster progression to AD. Cohort-wide studies have demonstrated that periods of economic recession and burden of disease at the time of birth are associated with lower cognitive function in older age.[41,42] Similarly, in a cohort of elderly men in Helsinki, lower birth weight, length, and head circumference were associated with lower cognitive ability at ages in the late 60s.[140] In childhood, low socioeconomic position, conflict at home, childhood health and family financial status are all associated with lower cognitive function later in life and SES and low childhood growth are associated with rate of decline in older age.[28,29,33,47,141] In instances of familial AD, stressful life events are associated with a reduced age of AD onset.[142] Directly related to pathology, Wilson, et al found that reports of emotional neglect in childhood are related to evidence of postmortem cerebral infarction.[143] The early-life period could be impactful on late life cognition and neuropathology via multiple mechanisms. First, as proposed by Wilson, et al. early childhood extending into the second decade of life is an important time in nervous system development.[144] Second, cognitively engaging and well resourced childhood environments could lay groundwork for other life course circumstances that promote the development of cognitive reserve, such as higher levels of education and SES, and engagement in cognitively stimulating activity throughout the life course. Finally, adverse childhood experiences could contribute to dysregulation of reward pathways and hormonal reactivity to stressors, which could predispose to poor health behaviors and intermediate health outcomes related to late life cognition.[33,145–147]

With the knowledge that the *APOE* ε4 allele is one of the strongest risk factors for late life adverse cognitive outcomes, studies have sought to investigate whether environmental factors can modify the relationship of the ε4 allele on cognitive outcomes. As when looking at

pathology, many of these studies have focused on possible resistance to the deleterious effect of the ε4 allele. As the mechanism by which the ε4 allele is related to adverse cognitive outcomes is via accumulation of neuropathology burden, modification of the effect of the allele could occur via either a diminution of such burden or via resistance to its presence. Shadlen et al. and Wang et al. have both observed that higher education is protective against cognitive decline and risk of dementia, respectively, among *APOE* ε4 allele carriers.[37,93] This is consistent with the education-as-resistance-to-pathology model demonstrated in Bennett et al.[50] Other studies have demonstrated non-genetic factors can modify the relationship of the *APOE* ε4 allele to neuropathology itself, including gender and age and lifetime cognitive activity.[148,149] However, there is also evidence that higher levels of education are actually associated with increased cognitive decline among *APOE* ε4 carriers.[36,95] This could be the result of higher baseline function of those with higher education, irrespective of *APOE* status, giving those individuals more opportunity for cognitive decline, or it could be that the adverse effects of the *APOE* ε4 allele are so strong that in the absence of other risk factors, which may be a characteristic of those with higher education, the association is more likely to be observed. Such a relationship has also been observed among residents living in neighborhoods with low levels of neighborhood social disorder; they were observed to have a strong association between the *APOE* ε4 allele and cognitive decline, compared to those in high social disorder neighborhoods with an ε4 allele.[150]

What is less explored is whether early-life environment can modify the impact of the *APOE* ε4 allele on cognitive function and decline and on neuropathology. There are a number of studies that have shown that head circumference, a measure thought to be reflective of early-life circumstance, interacts with the *APOE* ε4 allele to effect cognitive reserve.[115–117,151] That is,

those with larger head circumference are more protected against the deleterious effects of the *APOE* ε4 allele on cognitive decline. We additionally were able to find two studies that showed that higher childhood SES was protective against risk of dementia attributable to the *APOE* ε4 allele and against lower cognitive function, whereas lower SES exacerbated this relationship.[119,120] This study seeks to add to this literature by specifically considering whether Adverse Childhood Experience modifies the association of the *APOE* ε4 allele with neuropathology and with cognitive function and decline. This study uses data from the Memory and Aging Project of the Rush Alzheimer's Disease Cohorts.

DATA AND METHOD

Subjects

This analysis uses data from the Memory and Aging Project (MAP) of the Rush Alzheimer's Disease Center Cohorts. The Rush Alzheimer's Disease Center (RADC) cohorts are longitudinal studies of older adults that seek to understand chronic conditions of aging, with particular emphasis on cognitive decline and Alzheimer's disease. The MAP study includes yearly clinical evaluation of cognitive and motor function, conducted in the place of residence. At baseline, all participants must be cognitively intact to the point to have the ability to sign an Anatomical Gift Act, acquiescing to brain donation to the study upon death. The MAP was initiated in 1997 and continues to enroll subjects.

All analyses were limited to white-identified subjects to limit confounding by genetic ancestry. We additionally excluded subjects with an ε2/ε4 allele, as there is evidence that the ε2 allele can be protective against AD and cognitive decline.[152,153] Additionally, subjects had to have data on ACEs, genetic data, and pathology data for those who are deceased. The analytic population thus consisted of 1,792 subjects; this includes all subjects who had cleaned data

available at the time of the data request from the RADC Research Resource Sharing Hub (September 2018). For analyses with primary AD pathology as the outcome, we additionally excluded individuals with possible AD (individuals with AD and another condition) and those with dementia due to another condition.

Cognition

Cognition is assessed yearly during an in-residence visit or, if needed, over the phone using a comprehensive battery of 21 tests of cognitive performance.[154–156] From these tests, separate summary scores can be constructed to assess global cognitive function as well as five cognitive domains (episodic memory, semantic memory, working memory, perceptual orientation, and perceptual speed). Summary scores are constructed by converting each test to a z-score and then averaging the z-scores (both within cognitive domain and globally).[155] Both the raw scores and summary scores are provided in the Rush data set; summary scores have been used extensively in previous literature on this cohort.[50,157–159]

Early-Life Environment

Adverse Childhood Experiences (ACEs) are used to represent early-life experiences. The ACE battery in MAP consist of a 16-item questionnaire which was adapted from previously used questionnaires used to evaluate adverse childhood experiences in other cohort studies.[160–162] All questions address experiences during the first 18 years of life. Rush researchers group the 16 items into five domains, based on a principal components analysis, which has been previously described.[163] The five factors are emotional neglect, parental intimidation, parental violence, family turmoil, and financial need. Table 1 includes each individual item, organized by domain, as well as response options.

Genes

RADC cohorts extract DNA from peripheral blood or frozen postmortem brain tissue. DNA was genotyped by Polymorphic DNA Technologies (Alameda, CA). Laboratory investigators were blinded to all clinical and pathologic data. About 80% of the ROS, MAP, and MARS/Clinical Core population have genotype data available. Indicators for allelic variation of the *APOE* gene are supplied from Rush, with indicators for number of copies for each allele.

Post-Mortem Pathology

Post-mortem evaluation follows procedures put forth by the National Alzheimer's Disease Coordinating Center (NACC)[164]. All pathologic assessments are performed at Rush, are blinded to clinical data, and are reviewed by a board-certified neuropathologist. A global measure of Alzheimer's disease pathology is derived by combining counts of three AD pathologies: neuritic plaques, diffuse plaques, and neurofibrillary tangles. These pathologies are assessed in five brain regions: midfrontal cortex, midtemporal cortex, inferior parietal cortex, entorhinal cortex, and hippocampus. The count for each region is scaled by dividing by the standard deviation for the population and each scaled measure is then averaged to form a summary measure for each pathology. The summary measures are averaged to yield the measure of global AD pathology[136]. We use the global AD pathology measure as well as the summary measure for each individual pathology. We also look at cardiovascular associated AD pathology: gross chronic infarcts and chronic micoinfarcts which are reported as present or absent. Gross infarcts are visible to the eye on fixed slabs; microinfarcts are assessed in a minimum of nine brain regions.[135]

Clinical diagnoses

Clinical diagnoses are made each year, based on 11 of the 21 cognitive tests as well as participant-demographic blinded assessment by a neuropsychologist, with final determination made by a clinician reviewing all the data. Neurocognitive clinical outcomes include: no cognitive impairment (NCI); mild cognitive impairment, with no other condition contributing to cognitive impairment (MCI); MCI with another condition contributing to cognitive impairment (MCI+); Alzheimer's disease dementia, with no other condition contributing to cognitive impairment (AD); AD, with another condition contributing to cognitive impairment (AD+); and other dementia (i.e. other primary cause of dementia with no clinical evidence of AD). In previous work looking at associations between *APOE* and cognitive impairment and decline and/or pathology, Rush researchers have classified individuals with AD and another condition thought to be contributing to cognitive impairment (e.g. stroke) as "probable AD".[129,165]

Latent Class Analysis.

We used the scales developed within each domain of the ACE questions to identify latent classes to understand whether level of neuropathology or cognitive decline varied by pattern of childhood experience.[166] Latent class analysis (LCA) is a method that identifies underlying homogenous, mutually exclusive, groupings within a heterogeneous population. We estimated models of one, two, and three latent classes on the five ACE subscales. We compared models using Akaike's Information Criteria (AIC) and Bayesian Information Criterion (BIC), where smaller AIC and BIC values indicated better fit. Classes membership was based on the estimated posterior probability for each respondent, assignment being made to the class for which the probability was greater than 0.50. If all probabilities were under 0.50, class membership was assigned based on the highest probability. Models were estimated using the all individuals in the

MAP cohort who had information on ACEs. We compare distribution of class membership in this full sample to the subsample who have data on pathology and *APOE* ε4 status. A number of recent studies have used LCA to identify classes of ACEs.[167–170]

Statistical Analysis

We use mixed-effects models to examine level of cognitive function and change in cognitive function over time by ACE class and ε4 status. We first fit a main effects model with indicators for follow-up year, an indicator for having an ε4 allele, and ACE class. Next, we introduced an interaction term between ε4 allele status and follow-up year, in order to observe the relationship between genetic risk and cognitive decline. We then fit a model to evaluate whether there is an association between ACE class and cognitive decline by adding an interaction term between follow-up year and ACE class. Finally, we fit a model to evaluate whether the association between the ε4 allele and cognitive decline varies by ACE class by including a three-way interaction between follow-up year, ACE class, and ε4 status. We fit these four models for the global cognitive score as well as for each cognitive domain that the score includes: episodic memory, perceptual orientation, processing speed, semantic memory, and working memory. All models are adjusted for age (centered at 78), sex, and an indicator for baseline evaluation to account for practice effects. We additionally evaluate whether any observed association between ACEs and cognitive outcomes, whether modified by genetic risk or not, are modified by educational attainment.

We used ordinary least squares regression to look at whether the early-life environment, operationalized as ACE class, modified the association between possessing an *APOE* ε4 risk allele and primary AD neuropathological outcomes including global AD pathology, neuritic plaques, diffuse plaques, and neurofibrillary tangles. For pathology models, in addition to any

described transformations, all linear outcomes are standardized to facilitate comparisons across pathology types. We first fit models to assess whether there was a direct association between ACE class membership and the pathology outcome, with an indicator for *APOE* ε4 status included in the model. We then fit models with an interaction term between ACE class membership and the *APOE* ε4 risk allele indicator to assess whether the association of the *APOE* ε4 allele and the pathological outcome varies by ACE class. Because some of the pathological outcomes are not normally distributed, we additionally modeled the main effects and the interaction via a three-step process. First, we used logistic regression with the outcome as presence or absence of the pathology. Second, for those with presence of pathology we used OLS regression with the standardized pathology outcome. Third, also among those with presence of pathology, we used OLS regression with the outcome transformed using the square root and also standardized.

For the cardiovascular AD pathology, gross chronic infarcts and microinfarcts as, we conducted a logistic regression analysis with presence or absence of infarcts as the outcome. All models were adjusted for age at death and sex.

RESULTS

Table 2 has descriptive statistics of the white Memory and Aging Project study participants as well as descriptive statistics of those who are deceased. Table 3 has study population averages of each domain in the Adverse Childhood Experiences battery. Table 4 shows pathology results from those deceased and with available pathology data.

In the latent class analysis, a three-class model had the lowest AIC and BIC. We interpret the three classes based on mean values of each domain scale within class membership and define a low ACE class (Low), a middle class, defined by reports of emotional neglect along with

higher averages of other domains (EN-Mid), and a class defined by high reports of all ACEs (High). Figure 1 shows the standardized scores of ACE domains across latent classes. In the full MAP cohort, the Low ACE class had the most subjects with 634 (43%), the EN-Mid class had 602 (41%), and the High ACE class had 238 (16%). The class distributions in the Low, EN-Mid, and High ACEs classes 509 (42%), 502 (42%), and 191 (16%) in those with genetic data and 225 (43%), 230 (44%), and 72 (14%) in those with genetic and pathology data. The distribution of ACE classes in the subpopulations are not different from the overall MAP cohort.

Tables 5a-f show the mixed-effect models for cognition on ACE class and *APOE* ε4 allele. In each table, Model A includes all main effects, Model B also includes a term for decline by *APOE* ε4 risk allele status, Model C adds terms for decline by ACE class, and Model D adds a term to assess whether the association between the ε4 allele and cognitive decline varies by ACE class.

For global cognition and all domains, except processing speed, ACE class is associated with level of cognitive function at age 78 (mean centered age), with both EN-Mid and High ACE class membership associated with progressively lower average cognitive function, respectively, compared to the Low ACE class.

ACE class is associated with cognitive decline for global cognitive function, episodic memory, and perceptual orientation. In each case, this association was driven by High ACE class having a slower rate of decline compared to the EN-Mid ACE class. In the case of global cognitive function, the rate of decline was -0.09 standard deviation units per follow-up year for the Low ACE class, -0.10 for the EN-Mid ACE class, and -0.07 for the High ACE class. This pattern was similar among episodic memory and perceptual orientation. When education is added to these models, the patterning and significance of associations persists, though the

adverse relationship between the High ACE group and cognitive function is somewhat attenuated (Supplemental Tables S1a-f).

There is no evidence that the association between having an *APOE* ε4 allele and average cognitive function varies by ACE class. While there was evidence that having an *APOE* ε4 risk allele was associated with higher levels of cognitive decline in global cognition and in all cognitive domains, there was no evidence that this association varied by ACE class.

Table 6 shows model results for the primary AD pathology models: global AD pathology, neuritic plaques, diffuse plaques, and neurofibrillary tangles. Class membership is not associated with any of the primary AD pathology. There is trending, but not statistically significant, evidence that there is variation in neuropathology, specifically neuritic plaques and neurofibrillary tangles, by class membership among those with an *APOE* ε 4 allele, compared to no variation among those without and ε4 allele. In particular, there is suggestive evidence that among *APOE* ε4 allele carriers, those in the EN-Mid ACE class are more likely to have neuritic plaques and neurofibrillary tangles compared to the Low ACE group. Figures 2 illustrate this difference in variation in neuritic plaques, neurofibrillary tangles, and, by extension, global pathology, but the lack of difference in diffuse plaques.

In the additional analyses, ACE class was not associated with presence of primary AD pathology, nor was there variation in the relationship of the ε4 risk allele and presence of AD pathology by ACE class. Neurofibiliary tangles are so prevalent among deceased subjects, that there was not sufficient variation to fit a logistic regression model for their presence/absence and, by extension, nor was there sufficient variation to fit a global AD pathology model. Among those *with* primary AD pathology and with outcomes transformed using their square root, a similar patterning of association was observed as was in the whole sample (Supplemental Tables S2a-c).

Table 7 shows model results for cardiovascular associated AD pathology. ACE class is independently associated with odds of gross chronic infarcts (p=0.04), driven by those in the EN-Mid group having a higher odds of showing evidence of infarct (OR=1.67, p=0.01), compared to the Low ACE group. Having an *APOE* ε4 allele does not appear to be associated with gross chronic infarcts in a model that includes ACE class. This could be due to lack of power, as in a model without ACE class, it does increase the odds of infarcts, and has been shown to in previous literature[135]. ACE class is also not a confounder for the relationship between the ε4 risk allele and gross chronic infarcts. In the interaction model, variation in penetrance of *APOE* ε4 allele by class membership is marginally significant (p=0.06). Table 8 shows the odds ratios and 95% confidence intervals for gross chronic infarction, by ACE class and *APOE* ε4 allele status, with Low ACE/no *APOE* ε4 allele as the referent group. There is trending evidence that having an *APOE* ε4 allele *and* being in the EN-Mid ACE class or High ACE class is associated with an increased odds of gross chronic infarcts.

DISCUSSION

In our cognitive function models, we observed that those in the EN-Mid and High ACE class had lower average cognitive function compared to the Low ACE class for global cognition and all subdomains except processing speed and also that those in the High ACE class had lower function than the EN-Mid class. We also observed that for global cognitive function, episodic memory, and perceptual orientation, those in the High ACE class had a slower rate of cognitive decline compared to those in the EN-Mid ACE class. We did not observe that ACE class membership modified the association between possession of an *APOE* ε4 risk allele and cognitive function or cognitive decline.

It is consistent with previous literature that early live environment broadly and childhood experiences, in particular, are associated with cognitive function later in life, but not necessarily with cognitive decline.[29,30,33,141,171] Our observation that those in the High ACE class had a slower rate of decline than those in the EN-Mid class may reflect this literature – this group could experience lower cognitive function earlier in life, and so have a more gradual decline throughout all of old age. The average age of the analytic sample is almost 80.

In our pathology models we found that the association of the *APOE* ε4 allele with primary Alzheimer's disease pathology does not significantly vary by our ACE latent class groupings. However, there was suggestive evidence that those in the EN-Mid class have more neuritic plaques and neurofibrillary tangles than those in the Low or High ACE class. If this is evidence of a true association, it is reasonable that it would not be observed in the diffuse plaques, as they are deposits that are commonly present in cognitively intact elderly individuals.[172]

In the models looking at cerebrovascular outcomes, we found that those in the EN-Mid class had increased odds of having gross infarcts, compared to the Low ACE class. There is evidence from the Rush data that childhood adversity is associated with cerebral infarction in older age.[143] Wilson, et al. found that increased childhood adversity, using the cumulative scale in the Memory and Aging Project, was associated with increased odds of gross infarcts and that this association was primarily driven by high scores in the subdomain of emotional neglect.[143] We present a comparable finding in this analysis, where in the main effects model, the EN-Mid group drives the association between ACE class and gross infarcts. However, in the same model we do not observe an association between possession of an *APOE* ε4 risk allele and gross

infarcts. This is contrary to prior findings, where the *APOE* ε4 risk allele is associated with postmortem evidence of gross infarcts.[135]

However, in the interaction model, we found that there is variation in the relationship between the *APOE* ε4 allele and gross infarcts by ACE class. This is primarily driven by a strong relationship between the High ACE class and odds of cross infarction among ε4 allele carriers, though there is suggestive evidence that those in the EN-Mid ACE class also have an increased odds, relative to the Low ACE class (OR=1.73, 95% CI: 0.90, 3.32). This evidence that the *APOE* ε4 allele is strongly associated with gross infarcts, but that the association varies by ACE class, does allay concerns about not observing an association in the main effects model.

Why might we observe that the ACE class associated with increased risk is the EN-Mid class in the main effects model whereas in the interaction model the High ACE class is associated with increased risk? It is possible that the pathways to disease are distinct in the two models. Wilson, et al. proposed that their observation that individuals reporting higher levels of emotional neglect could have experienced –dysregulation of psychological and cognitive development, leading to risk associated behaviors and poor physical health, which are risk factors for cerebral infarcts.[143] In the interaction model, those in the High ACE class may have altered stress regulatory pathways and subsequent biological functioning. This could interact with the risk of having an *APOE* ε4 allele for cardiovascular outcomes, in particular, to increase risk of chronic gross infarcts observed in postmortem pathological evaluation. This pathway is buoyed by evidence that individuals who report high overall levels of ACEs are more likely to have neuroticism as personality type which itself is more highly associated with cardiovascular health outcomes.[173–175] The number of people in the High ACE class who also have an ε4 allele is small, so there is a lack of precision in this estimation.

Strengths of this study include high rates of follow-up, an extensive multi-domain cognitive measure, and inclusion of post-mortem neuropathology data. Adverse childhood experiences was evaluated with a previously established scale, although the reports are retrospective in nature.

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Table 3.1: Adverse Childhood Experience Items by Domain in the Rush Memory and Aging Project

Domain	Items	Response Options
Emotional Neglect	When you were growing up… was there someone in your family who helped you feel important or special? did you feel loved? did people in your family feel close to each other? was your family a source of strength and support to you? did you know there was someone there to take care of you and protect you? how often was there someone to take you to the doctor if you needed it?	Not at all, somewhat, moderately so, very much so
Family Need	When you were growing up, how often… was there not enough to eat? did you have to wear dirty clothes?	Never, rarely, sometimes, often, always
Parental Intimidation	When you were growing up, how often did an adult living in (or visiting) your home… say mean or hurtful things to you? act in a way that made you afraid you might be physically hurt? push, grab, slap, or throw something at you? argue with each other?	Never, rarely, sometimes, often, always
Parental Violence	When you were growing up, how often… were you punished with a belt, board, cord, or some other hard object? did physical blows occur between adults living in (or visiting) your home?	Never, rarely, sometimes, often, always
Family Problems and Separation	When you were growing up… Family problems: was a household member depressed or mentally ill? did a household member attempt suicide? was a household member a problem drinker or alcoholic? did a household member go to prison? Family separation: were you ever hospitalized for two weeks or more? did you ever have an experience that was so frightening that you thought about it for years? were you ever separated from your mother for a year or more? did your parents ever separate or divorce?	Yes, no

Table 3.2: Descriptive Statistics of Memory and Aging Project subjects (N=2,687)

	MAP (n=1,792)	MAP Deceased (n=895)
	mean (sd) or N(%)	mean (sd) or N(%)
Age at baseline	80.4 (7.3)	83.1 (5.9)
Male	483 (27%)	279 (31%)
Education (years)	14.8 (3.3)	14.5 (3.0)
Age at death	-	89.8 (6.2)
Have genetic data	1,500 (83.7%)	851 (95.1%)
Any E4 Allele	324 (22%)	181 (22%)

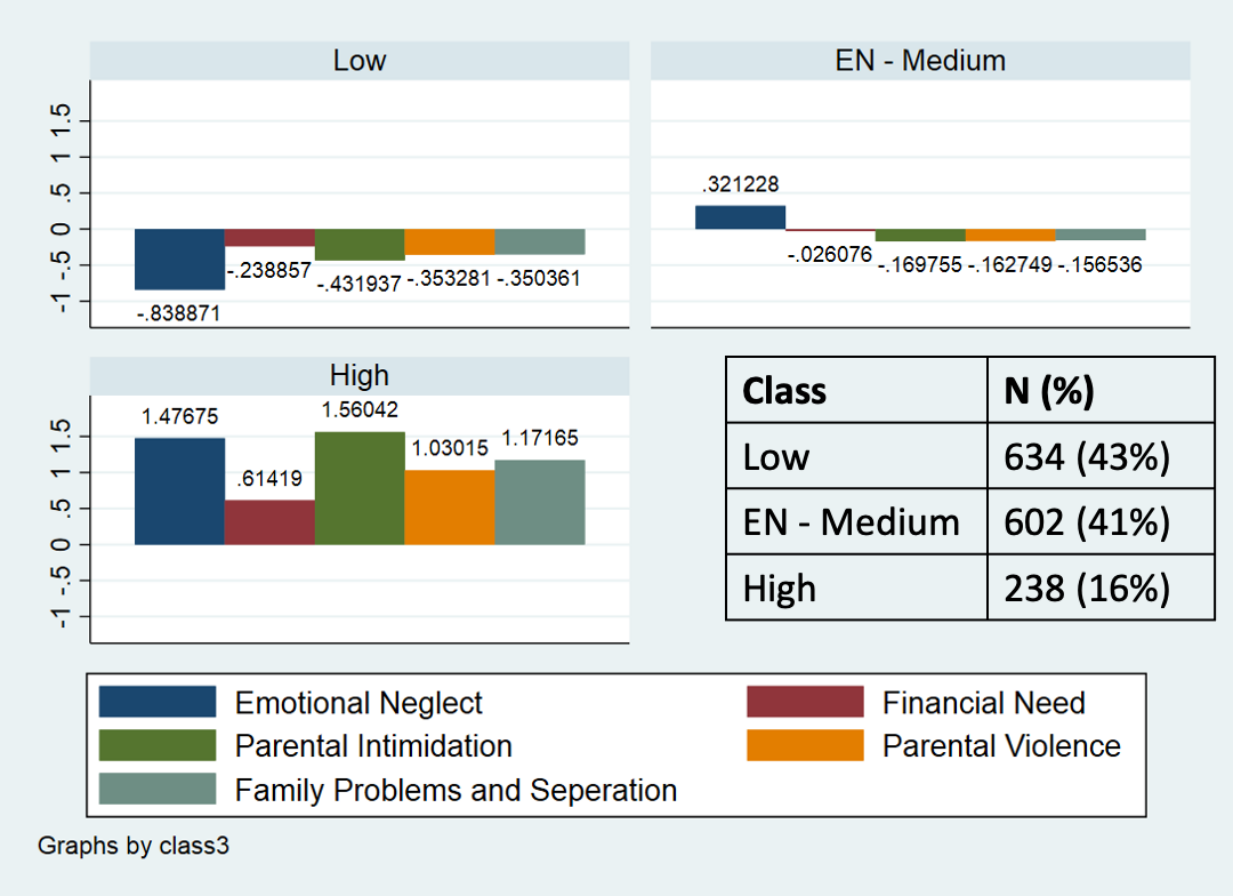
Table 3.3: Summary of Adverse Childhood Experiences in the Rush Memory and Aging Project (N=2,121)

	MAP (n=1,474)	MAP Deceased (n=647)
Domain (Scale range)	mean (sd)	mean (sd)
Emotional Neglect (0-18)	4.1 (4.2)	4.0 (4.1)
Financial Need (0-8)	0.8 (1.3)	0.8 (1.4)
Parental Intimidation (0-16)	1.7 (2.5)	2.5 (2.3)
Parental Violence (0-8)	0.7 (1.1)	0.6 (1.0)
Family Problems and Separation (0-8)	1.0 (1.2)	0.9 (1.1)

Table 3.4: Primary Alzheimer's Disease Pathology and Cardiovascular AD Pathology in the Rush Memory and Aging Project

	MAP with Pathology (n=740)	
	N(%)	mean (sd)
Alzheimer's Disease Pathology - Primary		
Diffuse Plaques (0-4.7)	609 (82%)	0.69 (0.73)
Neuritic Plaques (0-4.1)	589 (80%)	0.87 (0.83)
Neurofibrillary Tangles (0-6.1)	729 (99%)	0.71 (0.84)
Global Pathology (0-3.2)	735 (99%)	0.76 (0.63)
Cardiovascular Alzheimer's Disease Pathology		
Gross Chronic Infarcts	273 (37%)	
Chronic Microinfarcts	218 (30%)	

Figure 3.1: Standardized scores of Adverse Childhood Experience domains across latent classes in the Rush Memory and Aging Project



Class	N (%)
Low	634 (43%)
EN - Medium	602 (41%)
High	238 (16%)

Table 3.5a: Mixed-effect models predicting global cognitive function and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,146)

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.09	[-0.10,-0.08]	<0.01	-0.08	[-0.09,-0.07]	<0.01	-0.08	[-0.09,-0.07]	<0.01	-0.08	[-0.09,-0.06]	<0.01
APOE ε4	-0.08	[-0.16,-0.01]	0.03	-0.08	[-0.15,-0.00]	0.04	-0.08	[-0.15,-0.00]	0.04	-0.02	[-0.13,0.10]	0.78
ACE Class												
EN-Mid	-0.07	[-0.14,-0.00]	0.04	-0.07	[-0.14,-0.00]	0.04	-0.07	[-0.14,-0.00]	0.04	-0.04	[-0.12,0.03]	0.25
High	-0.21	[-0.30,-0.11]	<0.01	-0.21	[-0.30,-0.11]	<0.01	-0.20	[-0.30,-0.11]	<0.01	-0.18	[-0.29,-0.08]	<0.01
APOE ε4 x FU Year				-0.05	[-0.07,-0.03]	<0.01	-0.05	[-0.07,-0.03]	<0.01	-0.05	[-0.08,-0.03]	<0.01
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.03,0.00]	0.16	-0.01	[-0.03,0.01]	0.20
High x FU Year							0.02	[-0.00,0.04]	0.06	0.02	[-0.00,0.04]	0.10
ACE Class x ε4												
EN-Mid x ε4										-0.12	[-0.29,0.04]	0.14
High x ε4										-0.09	[-0.31,0.12]	0.40
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										0.00	[-0.04,0.04]	0.96
High x ε4 x FU Year										0.00	[-0.05,0.05]	0.95
Constant	0.45	[0.40,0.50]		0.45	[0.39,0.50]		0.45	[0.39,0.50]		0.43	[0.37,0.49]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Table 3.5b: Mixed-effect models predicting episodic memory and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,146)

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.08	[-0.09,-0.07]	<0.01	-0.07	[-0.08,-0.06]	<0.01	-0.07	[-0.09,-0.06]	<0.01	-0.07	[-0.09,-0.06]	<0.01
APOE ε4	-0.19	[-0.29,-0.10]	<0.01	-0.18	[-0.27,-0.08]	<0.01	-0.18	[-0.27,-0.08]	<0.01	-0.09	[-0.24,0.05]	0.19
ACE Class												
EN-Mid	-0.09	[-0.17,-0.00]	0.05	-0.08	[-0.17,-0.00]	0.05	-0.08	[-0.17,0.00]	0.05	-0.05	[-0.14,0.04]	0.30
High	-0.22	[-0.33,-0.10]	<0.01	-0.22	[-0.33,-0.10]	<0.01	-0.22	[-0.34,-0.10]	<0.01	-0.19	[-0.32,-0.06]	<0.01
APOE ε4 x FU Year				-0.06	[-0.08,-0.04]	<0.01	-0.06	[-0.08,-0.04]	<0.01	-0.06	[-0.09,-0.03]	<0.01
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.02,0.01]	0.46	-0.01	[-0.03,0.01]	0.54
High x FU Year							0.03	[0.01,0.05]	0.01	0.02	[-0.00,0.05]	0.10
ACE Class x ε4												
EN-Mid x ε4										-0.16	[-0.37,0.05]	0.13
High x ε4										-0.13	[-0.40,0.14]	0.35
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										0.00	[-0.05,0.04]	0.88
High x ε4 x FU Year										0.03	[-0.03,0.09]	0.29
Constant		0.51	[0.44,0.58]	0.50	[0.44,0.57]		0.50	[0.44,0.57]		0.49	[0.41,0.56]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Table 3.5c: Mixed-effect models predicting perceptual orientation and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,140)

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.04	[-0.05,-0.03]	<0.01	-0.04	[-0.04,-0.03]	<0.01	-0.03	[-0.04,-0.02]	<0.01	-0.03	[-0.04,-0.02]	<0.01
APOE ε4	0.00	[-0.09,0.09]	0.98	0.04	[-0.06,0.14]	0.39	0.05	[-0.05,0.15]	0.37	0.10	[-0.05,0.25]	0.21
ACE Class												
EN-Mid	-0.08	[-0.16,0.01]	0.07	-0.08	[-0.16,0.01]	0.07	-0.05	[-0.14,0.04]	0.28	-0.03	[-0.13,0.07]	0.52
High	-0.27	[-0.39,-0.16]	<0.01	-0.27	[-0.39,-0.16]	<0.01	-0.31	[-0.43,-0.19]	<0.01	-0.28	[-0.42,-0.14]	<0.01
APOE ε4 x FU Year				-0.02	[-0.03,-0.00]	0.01	-0.02	[-0.03,-0.00]	0.01	-0.02	[-0.04,-0.00]	0.04
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.02,0.00]	0.08	-0.01	[-0.03,0.00]	0.06
High x FU Year							0.01	[-0.00,0.03]	0.11	0.01	[-0.00,0.03]	0.15
ACE Class x ε4												
EN-Mid x ε4										-0.08	[-0.29,0.14]	0.50
High x ε4										-0.13	[-0.42,0.16]	0.39
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										0.01	[-0.02,0.04]	0.48
High x ε4 x FU Year										0.00	[-0.04,0.04]	0.91
Constant	0.31	[0.24,0.37]		0.29	[0.22,0.36]		0.29	[0.21,0.36]		0.27	[0.19,0.35]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Table 3.5d: Mixed-effect models predicting processing speed and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,143)

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.11	[-0.12,-0.11]	<0.01	-0.11	[-0.12,-0.10]	<0.01	-0.11	[-0.12,-0.09]	<0.01	-0.11	[-0.12,-0.09]	<0.01
APOE ε4	-0.11	[-0.22,0.01]	0.07	-0.08	[-0.19,0.04]	0.19	-0.08	[-0.19,0.04]	0.19	-0.04	[-0.21,0.13]	0.67
ACE Class												
EN-Mid	-0.03	[-0.13,0.08]	0.62	-0.03	[-0.13,0.08]	0.63	-0.02	[-0.12,0.09]	0.77	0.00	[-0.11,0.12]	0.99
High	-0.12	[-0.26,0.02]	0.10	-0.12	[-0.26,0.02]	0.10	-0.13	[-0.27,0.01]	0.07	-0.12	[-0.28,0.04]	0.14
APOE ε4 x FU Year				-0.03	[-0.05,-0.01]	<0.01	-0.03	[-0.05,-0.01]	<0.01	-0.03	[-0.06,-0.00]	0.02
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.03,0.01]	0.20	-0.01	[-0.03,0.01]	0.19
High x FU Year							0.02	[-0.01,0.04]	0.15	0.02	[-0.01,0.04]	0.13
ACE Class x ε4												
EN-Mid x ε4										-0.08	[-0.33,0.17]	0.54
High x ε4										-0.05	[-0.38,0.28]	0.77
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										0.01	[-0.03,0.05]	0.71
High x ε4 x FU Year										-0.01	[-0.06,0.04]	0.60
Constant	0.41	[0.33,0.49]		0.40	[0.32,0.48]		0.39	[0.31,0.48]		0.39	[0.29,0.47]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Table 3.5e: Mixed-effect models predicting semantic memory and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,143)

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.08	[-0.08,-0.07]	<0.01	-0.07	[-0.08,-0.06]	<0.01	-0.07	[-0.08,-0.05]	<0.01	-0.07	[-0.08,-0.05]	<0.01
APOE ε4	-0.07	[-0.16,0.02]	0.13	-0.03	[-0.12,0.06]	0.48	-0.03	[-0.12,0.06]	0.49	0.04	[-0.10,0.17]	0.61
ACE Class												
EN-Mid	-0.07	[-0.15,0.01]	0.08	-0.07	[-0.15,0.01]	0.09	-0.06	[-0.15,0.02]	0.12	-0.02	[-0.11,0.07]	0.63
High	-0.15	[-0.26,-0.04]	0.01	-0.15	[-0.26,-0.04]	0.01	-0.16	[-0.27,-0.05]	0.01	-0.18	[-0.31,-0.05]	0.01
APOE ε4 x FU Year				-0.04	[-0.06,-0.03]	<0.01	-0.04	[-0.06,-0.03]	<0.01	-0.04	[-0.07,-0.02]	<0.01
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.02,0.01]	0.35	-0.01	[-0.03,0.01]	0.32
High x FU Year							0.01	[-0.01,0.04]	0.19	0.02	[-0.01,0.04]	0.14
ACE Class x ε4												
EN-Mid x ε4										-0.20	[-0.40,-0.01]	0.04
High x ε4										0.08	[-0.18,0.34]	0.55
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										0.01	[-0.03,0.05]	0.69
High x ε4 x FU Year										-0.02	[-0.07,0.03]	0.47
Constant	0.43	[0.37,0.50]		0.43	[0.36,0.49]		0.42	[0.36,0.49]		0.41	[0.37,0.47]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Table 3.5f: Mixed-effect models predicting working memory and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,144)

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.06	[-0.07,-0.06]	<0.01	-0.05	[-0.06,-0.05]	<0.01	-0.05	[-0.06,-0.04]	<0.01	-0.05	[-0.06,-0.04]	<0.01
APOE ε4	-0.06	[-0.15,0.04]	0.24	0.01	[-0.08,0.11]	0.78	0.01	[-0.08,0.11]	0.77	0.02	[-0.13,0.16]	0.80
ACE Class												
EN-Mid	-0.13	[-0.22,-0.05]	<0.01	-0.13	[-0.22,-0.05]	<0.01	-0.11	[-0.20,-0.02]	0.01	-0.10	[-0.20,-0.01]	0.04
High	-0.17	[-0.29,-0.06]	<0.01	-0.17	[-0.28,-0.06]	<0.01	-0.17	[-0.29,-0.05]	0.01	-0.18	[-0.32,-0.05]	0.01
APOE ε4 x FU Year				-0.03	[-0.05,-0.02]	<0.01	-0.04	[-0.05,-0.02]	<0.01	-0.02	[-0.05,-0.00]	0.02
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.02,0.00]	0.06	-0.01	[-0.02,0.00]	0.19
High x FU Year							0.00	[-0.02,0.02]	0.94	0.01	[-0.01,0.03]	0.42
ACE Class x ε4												
EN-Mid x ε4										-0.04	[-0.25,0.17]	0.72
High x ε4										0.07	[-0.21,0.35]	0.62
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										-0.01	[-0.04,0.02]	0.45
High x ε4 x FU Year										-0.04	[-0.08,0.00]	0.07
Constant	0.35	[0.28,0.41]		0.33	[0.26,0.40]		.032	[0.25,0.39]		0.31	[0.24,0.39]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Table 3.6: OLS regression models predicting primary Alzheimer's disease pathology by ACE Class and *APOE* ε4 status in the Rush Memory and Aging Project (n=490)

	Main Effects Model			**Interaction Model**		
	B	95% CI	p-value	B	95% CI	p-value
Global AD Pathology						
ACE Class						
EN-Mid	0.07	[-0.10,0.24]	0.41	0.00	[-0.20,0.19]	0.97
High	0.06	[-0.20,0.31]	0.66	0.04	[-0.25,0.33]	0.78
APOE ε4	0.78	[0.58,0.97]	<0.01	0.62	[0.33,0.90]	<0.01
ACE Class x ε4						
EN-Mid x ε4				0.35	[-0.06,0.77]	0.09
High x ε4				0.07	[-0.55,0.70]	0.81
Constant	-2.07	[-3.29,-0.86]	0.00	-2.11	[-3.33,-0.89]	0.00
Neuritic Plaques						
ACE Class						
EN-Mid	0.08	[-0.10,0.26]	0.38	0.00	[-0.20,0.19]	0.96
High	0.08	[-0.19,0.34]	0.57	0.07	[-0.23,0.37]	0.66
APOE ε4	0.71	[0.51,0.91]	<0.01	0.53	[0.23,0.84]	<0.01
ACE Class x ε4						
EN-Mid x ε4				0.39	[-0.04,0.82]	0.08
High x ε4				0.06	[-0.59,0.70]	0.87
Constant	-1.44	[-2.71,-0.18]	0.03	-1.48	[-2.75,-0.22]	0.02
Diffuse Plaques						
ACE Class						
EN-Mid	0.04	[-0.12,0.19]	0.66	0.04	[-0.14,0.22]	0.64
High	0.15	[-0.09,0.39]	0.21	0.14	[-0.13,0.41]	0.31
APOE ε4	0.35	[0.17,0.53]	<0.01	0.36	[0.09,0.63]	0.01
ACE Class x ε4						
EN-Mid x ε4				-0.03	[-0.42,0.35]	0.86
High x ε4				0.05	[-0.53,0.63]	0.85
Constant	-1.88	[-3.01,-0.75]	0.00	-1.88	[-3.01,-0.74]	0.00
Neurofibrillary Tangles						
ACE Class						
EN-Mid	0.05	[-0.13,0.23]	0.57	-0.05	[-0.25,0.16]	0.65
High	-0.10	[-0.37,0.18]	0.49	-0.11	[-0.42,0.20]	0.48
APOE ε4	0.75	[0.55,0.96]	<0.01	0.55	[0.24,0.86]	<0.01
ACE Class x ε4						
EN-Mid x ε4				0.46	[0.02,0.90]	0.04
High x ε4				0.07	[-0.60,0.73]	0.84
Constant	-1.57	[-2.87,-0.28]	0.02	-1.62	[-2.91,-0.33]	0.01

*Models are adjusted for age at death and sex. Outcomes are standardized.

Figure 3.2: Linear prediction of pathology by ACE Class and *APOE* ε4 Status in the Rush Memory and Aging Project

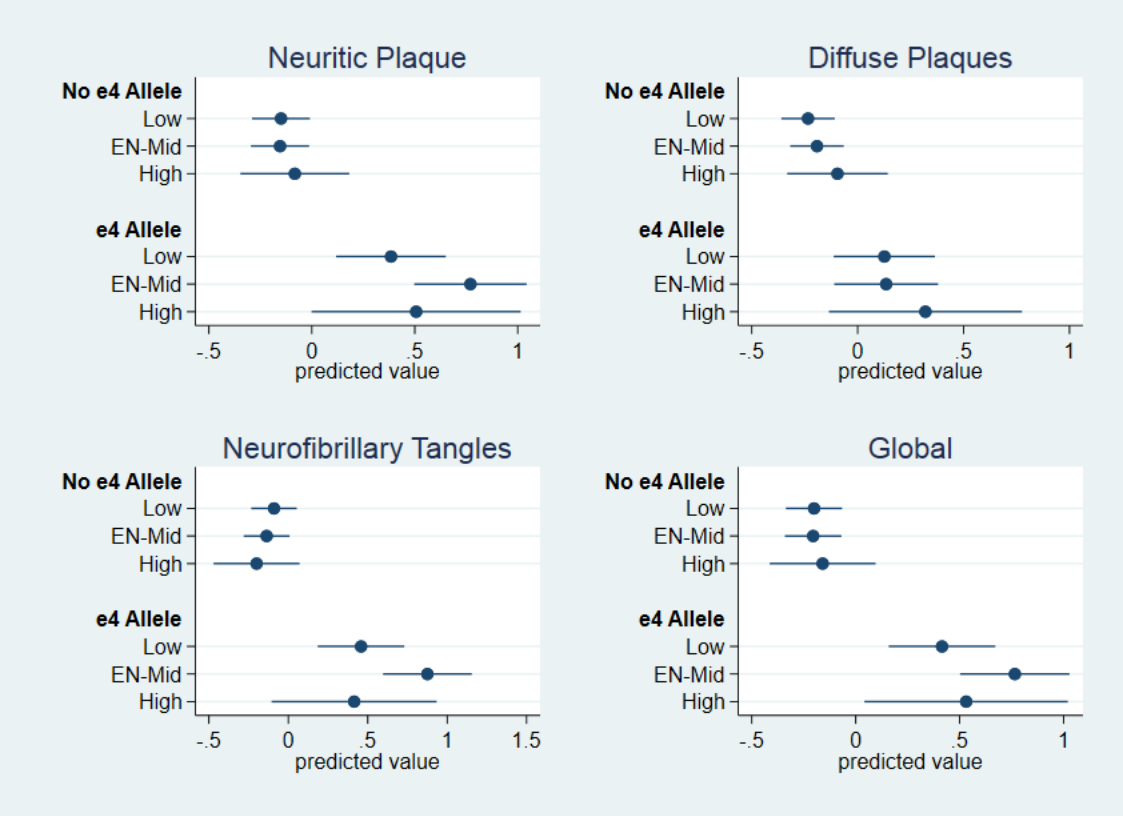


Table 3.7: Logistic regression models predicting cardiovascular Alzheimer's disease pathology by ACE Class and *APOE* ε4 status in the Rush Memory and Aging Project (N=489)

	Main Effects Model			**Interaction Model**		
	OR	95% CI	p-value	B	95% CI	p-value
Gross Chronic Infarctions						
ACE Class						
EN-Mid	1.67	[1.14,2.46]	0.01	1.57	[1.02,2.42]	0.04
High	1.32	[0.76,2.31]	0.33	0.89	[0.46,1.70]	0.72
APOE ε4	1.20	[0.78,1.85]	0.41	0.82	[0.41,1.64]	0.57
ACE Class x *APOE* ε4						
EN-Mid x *APOE* ε4				1.35	[0.52,3.47]	0.54
High x *APOE* ε4				5.98	[1.47,24.38]	0.01
Chronic Microinfarctions						
ACE Class						
EN-Mid	1.02	[0.68,1.53]	0.92	1.06	[0.68,1.67]	0.79
High	1.15	[0.65,2.05]	0.63	0.94	[0.49,1.84]	0.87
APOE ε4	0.97	[0.61,1.54]	0.91	0.93	[0.46,1.88]	0.84
ACE Class x *APOE* ε4						
EN-Mid x *APOE* ε4				0.81	[0.30,2.24]	0.69
High x *APOE* ε4				2.37	[0.61,9.31]	0.21

*Models are adjusted for age at death and sex.

Table 3.8: Odds ratios for gross chronic infarctions by ACE class and *APOE* ε4 allele status in the Rush Memory and Aging Project (N=489)

	No *APOE* ε4 Risk Allele			*APOE* ε4 Risk Allele		
	N	OR	95% CI	N	OR	95% CI
ACE Class						
Low	175	REF	REF	49	0.82	[0.41,1.64]
EN-Mid	180	1.57	[1.02,2.42]	49	1.73	[0.90, 3.32]
High	57	0.89	[0.46,1.70]	15	4.34	[1.41, 13.39]

Supplemental Table 3.1a: Mixed-effect models predicting global cognitive function level and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,146), with education

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.09	[-0.10,-0.08]	<0.01	-0.08	[-0.09,-0.07]	<0.01	-0.08	[-0.09,-0.07]	<0.01	-0.08	[-0.09,-0.06]	<0.01
APOE ε4	-0.12	[-0.19,-0.05]	<0.01	-0.11	[-0.18,-0.04]	<0.01	-0.11	[-0.18,-0.04]	<0.01	-0.05	[-0.15,0.06]	0.39
ACE Class												
EN-Mid	-0.03	[-0.09,0.03]	0.32	-0.03	[-0.09,0.03]	0.33	-0.03	[-0.09,0.03]	0.34	0.00	[-0.08,0.07]	0.89
High	-0.12	[-0.21,-0.03]	0.01	-0.12	[-0.21,-0.03]	0.01	-0.12	[-0.21,-0.03]	0.01	-0.10	[-0.19,0.00]	0.06
APOE ε4 x FU Year				-0.05	[-0.07,-0.03]	<0.01	-0.05	[-0.07,-0.03]	<0.01	-0.05	[-0.08,-0.03]	<0.01
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.03,0.00]	0.17	-0.01	[-0.03,0.01]	0.20
High x FU Year							0.02	[-0.00,0.04]	0.07	0.02	[-0.00,0.04]	0.10
ACE Class x ε4												
EN-Mid x ε4										-0.12	[-0.27,0.03]	0.12
High x ε4										-0.11	[-0.31,0.09]	0.29
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										0.00	[-0.03,0.04]	0.87
High x ε4 x FU Year										0.00	[-0.05,0.05]	0.96
Education	0.06	[0.05,0.07]	<0.01	0.06	[0.05,0.07]	<0.01	0.06	[0.05,0.07]	<0.01	0.06	[0.05,0.07]	<0.01
Constant	0.54	[0.49,0.59]		0.54	[0.48,0.59]		0.53	[0.48,0. 59]		0.52	[0.47,0. 57]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Supplemental Table 3.1b: Mixed-effect models predicting episodic memory and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,146), with education

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.08	[-0.09,-0.07]	<0.01	-0.07	[-0.08,-0.06]	<0.01	-0.07	[-0.09,-0.06]	<0.01	-0.07	[-0.09,-0.06]	<0.01
APOE ε4	-0.22	[-0.31,-0.13]	<0.01	-0.20	[-0.30,-0.11]	<0.01	-0.20	[-0.30,-0.11]	<0.01	-0.12	[-0.26,0.02]	0.10
ACE Class												
EN-Mid	-0.06	[-0.14,0.03]	0.19	-0.05	[-0.14,0.03]	0.20	-0.05	[-0.14,0.03]	0.21	-0.02	[-0.11,0.07]	0.68
High	-0.15	[-0.26,-0.03]	0.01	-0.15	[-0.26,-0.03]	0.01	-0.15	[-0.27,-0.04]	0.01	-0.12	[-0.25,0.01]	0.07
APOE ε4 x FU Year	-0.06	[-0.08,-0.04]	<0.01	-0.06	[-0.08,-0.04]	<0.01	-0.06	[-0.09,-0.03]	<0.01			
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.02,0.01]	0.46	-0.01	[-0.03,0.01]	0.53
High x FU Year							0.03	[0.01,0.05]	0.01	0.02	[-0.00,0.05]	0.10
ACE Class x ε4												
EN-Mid x ε4										-0.16	[-0.36,0.04]	0.12
High x ε4										-0.14	[-0.41,0.12]	0.29
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										0.00	[-0.04,0.04]	0.92
High x ε4 x FU Year										0.03	[-0.02,0.09]	0.27
Education	0.05	[0.03,0.06]	<0.01	0.05	[0.03,0.06]	<0.01	0.05	[0.03,0.06]	<0.01	0.05	[0.03,0.06]	<0.01
Constant	0.58	[0.51,0.65]		0.58	[0.51,0.65]		0.58	[0.51,0.65]		0.56	[0.49,0.63]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Supplemental Table 3.1c: Mixed-effect models predicting perceptual orientation and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,140), with education

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.04	[-0.05,-0.03]	<0.01	-0.04	[-0.04,-0.03]	<0.01	-0.03	[-0.04,-0.02]	<0.01	-0.03	[-0.04,-0.02]	<0.01
APOE ε4	-0.05	[-0.14,0.04]	0.24	-0.01	[-0.10,0.09]	0.91	0.00	[-0.10,0.09]	0.94	0.05	[-0.09,0.19]	0.47
ACE Class												
EN-Mid	-0.02	[-0.10,0.05]	0.53	-0.03	[-0.10,0.05]	0.52	0.00	[-0.08,0.09]	0.91	0.02	[-0.07,0.11]	0.66
High	-0.16	[-0.26,-0.05]	<0.01	-0.16	[-0.26,-0.05]	<0.01	-0.19	[-0.31,-0.08]	<0.01	-0.15	[-0.29,-0.02]	0.02
APOE ε4 x FU Year				-0.02	[-0.03,-0.00]	0.02	-0.02	[-0.03,-0.00]	0.01	-0.02	[-0.04,-0.00]	0.04
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.02,0.00]	0.08	-0.01	[-0.03,0.00]	0.06
High x FU Year							0.01	[-0.00,0.03]	0.11	0.01	[-0.00,0.03]	0.14
ACE Class x ε4												
EN-Mid x ε4										-0.07	[-0.28,0.13]	0.48
High x ε4										-0.16	[-0.44,0.11]	0.24
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										0.01	[-0.02,0.04]	0.54
High x ε4 x FU Year										0.00	[-0.04,0.03]	0.90
Education	0.08	[0.07,0.10]	<0.01	0.08	[0.07,0.10]	<0.01	0.08	[0.07,0.10]	<0.01	0.08	[0.07,0.10]	<0.01
Constant	0.42	[0.35,0.48]		0.41	[0.34,0.49]		0.40	[0.33,0.47]		0.39	[0.32,0.46]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Supplemental Table 3.1d: Mixed-effect models predicting processing speed and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,143), with education

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.11	[-0.12,-0.11]	<0.01	-0.11	[-0.12,-0.10]	<0.01	-0.11	[-0.12,-0.09]	<0.01	-0.10	[-0.12,-0.09]	<0.01
APOE ε4	-0.15	[-0.26,-0.04]	0.01	-0.12	[-0.23,-0.01]	0.04	-0.12	[-0.23,-0.00]	0.04	-0.07	[-0.24,0.09]	0.38
ACE Class												
EN-Mid	0.02	[-0.08,0.12]	0.71	0.02	[-0.08,0.12]	0.70	0.03	[-0.07,0.13]	0.56	0.05	[-0.07,0.16]	0.42
High	-0.02	[-0.16,0.12]	0.78	-0.02	[-0.16,0.12]	0.78	-0.03	[-0.17,0.10]	0.63	-0.02	[-0.17,0.14]	0.83
APOE ε4 x FU Year				-0.03	[-0.05,-0.01]	<0.01	-0.03	[-0.05,-0.01]	<0.01	-0.03	[-0.06,-0.00]	0.02
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.03,0.01]	0.19	-0.01	[-0.03,0.01]	0.18
High x FU Year							0.02	[-0.01,0.04]	0.15	0.02	[-0.01,0.04]	0.13
ACE Class x ε4												
EN-Mid x ε4										-0.08	[-0.32,0.17]	0.53
High x ε4										-0.07	[-0.39,0.25]	0.66
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										0.01	[-0.03,0.05]	0.69
High x ε4 x FU Year										-0.01	[-0.06,0.04]	0.62
Education	0.07	[0.05,0.08]	<0.01	0.07	[0.05,0.08]	<0.01	0.07	[0.05,0.08]	<0.01	0.07	[0.05,0.08]	<0.01
Constant	0.51	[0.43,0.59]		0.50	[0.42,0.59]		0.50	[0.42,0.58]		0.49	[0.41,0.58]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Supplemental Table 3.1e: Mixed-effect models predicting semantic memory and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,143), with education

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.08	[-0.08,-0.07]	<0.01	-0.07	[-0.08,-0.06]	<0.01	-0.07	[-0.08,-0.05]	<0.01	-0.07	[-0.08,-0.05]	<0.01
APOE ε4	-0.12	[-0.20,-0.03]	0.01	-0.08	[-0.16,0.01]	0.07	-0.08	[-0.16,0.01]	0.07	-0.01	[-0.13,0.12]	0.92
ACE Class												
EN-Mid	-0.02	[-0.09,0.06]	0.66	-0.02	[-0.09,0.06]	0.68	-0.01	[-0.08,0.06]	0.79	0.03	[-0.05,0.11]	0.47
High	-0.04	[-0.14,0.07]	0.50	-0.03	[-0.14,0.07]	0.51	-0.04	[-0.15,0.06]	0.39	-0.06	[-0.17,0.06]	0.34
APOE ε4 x FU Year				-0.04	[-0.06,-0.03]	<0.01	-0.05	[-0.06,-0.03]	<0.01	-0.05	[-0.07,-0.02]	0.00
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.02,0.01]	0.37	-0.01	[-0.03,0.01]	0.32
High x FU Year							0.01	[-0.01,0.04]	0.20	0.02	[-0.01,0.04]	0.14
ACE Class x ε4												
EN-Mid x ε4										-0.20	[-0.38,-0.02]	0.03
High x ε4										0.04	[-0.20,0.29]	0.72
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										0.01	[-0.03,0.05]	0.65
High x ε4 x FU Year										-0.02	[-0.07,0.03]	0.49
Education	0.08	[0.07,0.09]	<0.01	0.08	[0.07,0.09]	<0.01	0.08	[0.07,0.09]	<0.01	0.08	[0.07,0.09]	<0.01
Constant	0.55	[0.49,0.61]		0.54	[0.48,0.60]		0.54	[0.48,0.60]		0.52	[0.46,0.59]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Supplemental Table 3.1f: Mixed-effect models predicting working memory and decline by ACE Class, *APOE* ε4, and follow-up year in the Rush Memory and Aging Project (N=1,144), with education

	Model A			Model B			Model C			Model D		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Follow-up Year	-0.06	[-0.07,-0.06]	<0.01	-0.05	[-0.06,-0.05]	<0.01	-0.05	[-0.06,-0.04]	<0.01	-0.05	[-0.06,-0.04]	<0.01
APOE ε4	-0.10	[-0.19,-0.01]	0.04	-0.02	[-0.12,0.07]	0.64	-0.02	[-0.12,0.07]	0.66	-0.01	[-0.15,0.13]	0.85
ACE Class												
EN-Mid	-0.10	[-0.18,-0.02]	0.02	-0.10	[-0.18,-0.02]	0.02	-0.07	[-0.15,0.01]	0.10	-0.06	[-0.16,0.03]	0.19
High	-0.09	[-0.20,0.02]	0.12	-0.09	[-0.20,0.02]	0.13	-0.09	[-0.20,0.03]	0.15	-0.10	[-0.23,0.04]	0.16
APOE ε4 x FU Year				-0.03	[-0.05,-0.02]	<0.01	-0.03	[-0.05,-0.02]	<0.01	-0.02	[-0.05,-0.00]	0.02
ACE Class x FU Year												
EN-Mid x FU Year							-0.01	[-0.02,0.00]	0.06	-0.01	[-0.02,0.00]	0.18
High x FU Year							0.00	[-0.02,0.02]	0.95	0.01	[-0.01,0.03]	0.43
ACE Class x ε4												
EN-Mid x ε4										-0.04	[-0.24,0.17]	0.73
High x ε4										0.04	[-0.23,0.32]	0.75
ACE Class x ε4 x FU Year												
EN-Mid x ε4 x FU Year										-0.01	[-0.04,0.02]	0.46
High x ε4 x FU Year										-0.04	[-0.08,0.00]	0.07
Education	0.06	[0.05,0.07]	<0.01	0.06	[0.05,0.07]	<0.01	0.06	[0.05,0.07]	<0.01	0.06	[0.05,0.07]	<0.01
Constant	0.43	[0.36,0.50]		0.41	[0.34,0.48]		0.40	[0.33,0.47]		0.40	[0.33,0.47]	

*Models are adjusted for age (mean centered – 78 years), sex, and an indicator for baseline evaluation to adjust for practice effects.

Supplemental Table 3.2a: Logistic regression models for presence of primary Alzheimer's disease pathology by ACE Class and *APOE* ε4 status in the Rush Memory and Aging Project (n=490)

	Main Effects Model			**Interaction Model**		
	OR	95% CI	p-value	OR	95% CI	p-value
Global AD Pathology – Models do not converge						
Neuritic Plaques						
ACE Class						
EN-Mid	0.93	[0.57,1.52]	0.77	0.89	[0.53,1.48]	0.65
High	0.96	[0.46,1.99]	0.91	0.97	[0.46,2.08]	0.94
APOE ε4	5.51	[2.32,13.07]	<0.01	4.38	[1.28,14.98]	0.02
ACE Class x ε4						
EN-Mid x ε4				1.85	[0.27,12.59]	0.53
High x ε4				0.88	[0.07,10.48]	0.92
Diffuse Plaques						
ACE Class						
EN-Mid	0.91	[0.54,1.55]	0.74	0.90	[0.52,1.57]	0.72
High	0.90	[0.41,1.94]	0.78	0.94	[0.42,2.11]	0.88
APOE ε4	5.10	[1.99,13.03]	<0.01	5.18	[1.19,22.58]	0.03
ACE Class x ε4						
EN-Mid x ε4				1.16	[0.14,9.35]	0.89
High x ε4				0.60	[0.04,8.26]	0.70
Neurofibrillary Tangles						
ACE Class						
EN-Mid	0.89	[0.16,4.83]	0.89	***Model does not converge***		
High	0.54	[0.08,3.55]	0.52			
APOE ε4	2.19	[0.26,18.57]	0.47			
ACE Class x ε4						
EN-Mid x ε4						
High x ε4						

*Models are adjusted for age at death and sex.

Supplemental Table 3.2b: ACE Class, *APOE* ε4, and primary Alzheimer's disease pathology among those with pathology outcomes in the Rush Memory and Aging Project

	Main Effects Model			**Interaction Model**		
	B	95% CI	p-value	B	95% CI	p-value
Global AD Pathology (n=488)						
ACE Class						
EN-Mid	0.07	[-0.10,0.24]	0.39	0.00	[-0.19,0.19]	1.00
High	0.07	[-0.19,0.33]	0.61	0.06	[-0.23,0.35]	0.70
APOE ε4	0.77	[0.58,0.97]	<0.01	0.62	[0.33,0.90]	<0.01
ACE Class x ε4						
EN-Mid x 4				0.35	[-0.07,0.76]	0.10
High x *APOE* ε4				0.06	[-0.57,0.68]	0.85
Constant	-1.97	[-3.20,-0.74]	<0.01	-2.01	[-3.24,-0.78]	<0.01
Neuritic Plaques (n=393)						
ACE Class						
EN-Mid	0.10	[-0.09,0.29]	0.32	0.01	[-0.22,0.23]	0.96
High	0.11	[-0.18,0.40]	0.45	0.10	[-0.23,0.44]	0.54
APOE ε4	0.53	[0.32,0.74]	<0.01	0.37	[0.06,0.68]	0.02
ACE Class x ε4						
EN-Mid x ε4				0.37	[-0.08,0.81]	0.1
High x ε4				0.03	[-0.64,0.70]	0.92
Constant	-0.49	[-1.88,0.90]	0.49	-0.54	[-1.94,0.85]	0.44
Diffuse Plaques (n=411)						
ACE Class						
EN-Mid	0.06	[-0.12,0.23]	0.52	0.07	[-0.13,0.27]	0.47
High	0.2	[-0.06,0.46]	0.14	0.18	[-0.12,0.49]	0.23
APOE ε4	0.23	[0.04,0.42]	0.02	0.25	[-0.03,0.53]	0.08
ACE Class x ε4						
EN-Mid x ε4				-0.06	[-0.47,0.34]	0.75
High x ε4				0.05	[-0.56,0.66]	0.87
Constant	-1.34	[-2.58,-0.11]	0.03	-1.33	[-2.57,-0.09]	0.04
Neurofibrillary Tangles (n=482)						
ACE Class						
EN-Mid	0.05	[-0.13,0.23]	0.60	-0.05	[-0.26,0.15]	0.61
High	-0.08	[-0.36,0.20]	0.57	-0.12	[-0.43,0.19]	0.46
APOE ε4	0.75	[0.55,0.96]	<0.01	0.53	[0.22,0.84]	<0.01
ACE Class x ε4						
EN-Mid x ε4				0.47	[0.03,0.91]	0.04
High x ε4				0.17	[-0.51,0.85]	0.63
Constant	-1.38	[-2.72,-0.04]	0.04	-1.44	[-2.78,-0.10]	0.03

*Models are adjusted for age at death and sex. Outcomes are standardized.

Supplemental Table 3.2c: ACE Class, *APOE* ε4, and primary Alzheimer's disease pathology among those with pathology (transformed to square root) in the Rush Memory and Aging Project

	Main Effects Model			**Interaction Model**		
	B	95% CI	p-value	B	95% CI	p-value
Global AD Pathology (n=488)						
ACE Class						
EN-Mid	0.08	[-0.09,0.25]	0.36	0.01	[-0.18,0.20]	0.92
High	0.09	[-0.17,0.35]	0.51	0.10	[-0.20,0.39]	0.52
APOE ε4	0.74	[0.54,0.93]	<0.01	0.60	[0.31,0.89]	<0.01
ACE Class x ε4						
EN-Mid x ε4				0.33	[-0.09,0.74]	0.12
High x ε4				-0.04	[-0.67,0.59]	0.90
Constant	-2.42	[-3.66,-1.18]	<0.01	-2.46	[-3.70,-1.22]	<0.01
Neuritic Plaques (n=393)						
ACE Class						
EN-Mid	0.09	[-0.07,0.25]	0.25	0.03	[-0.16,0.21]	0.78
High	0.10	[-0.14,0.34]	0.41	0.11	[-0.17,0.38]	0.44
APOE ε4	0.42	[0.25,0.59]	<0.01	0.31	[0.06,0.56]	0.02
ACE Class x ε4						
EN-Mid x ε4				0.26	[-0.10,0.63]	0.15
High x ε4				-0.03	[-0.58,0.52]	0.91
Constant	-0.54	[-1.68,0.60]	0.35	-0.58	[-1.73,0.56]	0.32
Diffuse Plaques (n=411)						
ACE Class						
EN-Mid	0.07	[-0.08,0.23]	0.36	0.08	[-0.10,0.26]	0.39
High	0.18	[-0.06,0.41]	0.14	0.18	[-0.10,0.45]	0.21
APOE ε4	0.27	[0.10,0.45]	<0.01	0.28	[0.03,0.54]	0.03
ACE Class x ε4						
EN-Mid x ε4				-0.02	[-0.39,0.34]	0.91
High x ε4				0.01	[-0.54,0.56]	0.97
Constant	-1.07	[-2.19,0.05]	0.06	-1.07	[-2.19,0.06]	0.06
Neurofibrillary Tangles (n=482)						
ACE Class						
EN-Mid	0.06	[-0.12,0.24]	0.52	-0.02	[-0.22,0.18]	0.85
High	-0.07	[-0.34,0.20]	0.62	-0.09	[-0.39,0.22]	0.58
APOE ε4	0.72	[0.51,0.92]	<0.01	0.55	[0.25,0.85]	<0.01
ACE Class x ε4						
EN-Mid x ε4				0.36	[-0.07,0.80]	0.1
High x ε4				0.08	[-0.59,0.75]	0.82
Constant	-2.32	[-3.63,-1.01]	<0.01	-2.37	[-3.68,-1.06]	<0.01

*Models are adjusted for age at death and sex. Outcomes are in square root and standardized.

CONCLUSION

Objectives

The aim of this dissertation was to explore relationships between genes, individual level environment, population level environment, and behavioral factors with cognitive health outcomes. Aim 1 stood apart from Aims 2 and 3 in that it looked at a temporally proximate risk to the cognitive outcomes under investigation. In the Aim 1, we look at the relationship of sleep characteristics to cognitive function and decline. In Aims 2 and 3, we situated our analyses in a lifecourse-perspective theoretical framework which posits that factors throughout development could impact disease onset and progression. In these aims, we looked at whether the early-life environment modified the relationship of the *APOE* ε4 allele to cognitive function and decline and to neuropathology related to dementias. We additionally explored whether such a modification, if observed, was attenuated by educational achievement. Aim 2 operationalized early-life environment as birth-year cohort, those born before the start of World War II and those born after. Aim 3 looked at individual early-life circumstances, specifically Adverse Childhood Experiences (ACEs). In all Aims, we looked at cognitive function as an outcome. In Aim 1, we also looked at cognitive change over a 5-year period which was operationalized as odds of cognitive decline. In Aims 2 and 3, we used Mixed-effect models to look at cognitive decline over time. In Aim 3, among deceased subjects, we were additionally able to look at neuropathology outcomes associated with cognitive impairment.

Aim 1 – Sleep Characteristics and Cognitive Function and Cognitive Decline among Older Adults

Aim 1 furthered literature showing more objective measures of sleep disruption to be important indicators of both cognitive function and cognitive decline. While it stands in contrast to studies that report associations between self-reported sleep and cognitive function and decline, the null finding alongside significant associations between actigraph measured sleep and cognitive outcomes is a strength of this paper. We also believe this study is the first to show differences by sex in the relationship between objective measures of sleep and cognitive outcomes. Our paper builds on previous work of single gender cohort studies of older adults that had reported different associations between actigraph sleep measurements and cognitive decline for men and women as well as studies that have observed differential associations by gender but in younger populations, relying on self-reported sleep, or focusing on sleep apnea as opposed to normal variation in sleep.

While the findings in the paper are novel, they also point to questions to be answered in future research. The observation that sleep disruption measures were more strongly associated with cognitive decline in men than in women needs to be replicated and potential pathways which explain this difference need to be explored. Although NSHAP did have a direct question about sleep apnea diagnosis at follow-up, apnea is underdiagnosed so this likely underestimates the prevalence. Future research should also look at the changes in sleep patterns over time and their relationships with cognitive function and decline. Such research would tell us whether changes in sleep characteristics associated with cognitive function and decline could, in turn, lead to improvements in cognitive function and decline. In other words, if disrupted sleep is diminished over time, would cognition cease to decline or even improve? This line of research

will inform possibilities for intervention related to sleep hygiene. NSHAP is well positioned to begin such an inquiry, with data on actigraph measures of sleep for follow-up. Ultimately though, other studies will have to fill in the gaps when it comes to addressing changes in sleep patterns over shorter time periods, as the time between waves in NSHAP is five years.

In contrast to the other two Aims, this paper assessed a potential risk factor for cognition function and decline which was temporally proximal to the outcome. There are three primary benefits to such an analysis. The first is that such assessment is logistically much more feasible. Second, the opportunities for intervention are much more achievable, whether in terms of prevention of the risk factor or of modification of the risk factor if the deleterious relationship can be reversed. Finally, temporally proximate assessment of risk is less subject to any recall bias if a risk factor that has previously been experienced is reported by the subject or to missing data or misclassification if the data is gathered from other data sources.

Aim 2 and Aim 3 – Gene by Early-life Environment Interaction on Cognitive Decline

The objective in these aims was to examine whether the strength of association between the *APOE* ε4 allele and cognitive function, decline, and neuropathology varied by early-life environment. While this overall objective was consistent across aims, the conceptualization and measurement of early-life environment is very different. The differences in these conceptualizations are reflected in what each measure might represent in terms of early-life environment and could explain some divergent findings between the two aims. Broadly speaking, the measure of early-life environment in Aim 2, birth-year cohort, is intended to represent broad cohort-wide environmental characteristics that have changed over time. In Aim 3, operationalizing early-life environment as Adverse Childhood Experiences (ACEs) is meant to

contrast this broad cohort-level measure with one that considers risk at the individual and familial level.

Birth-year cohort has been used as a marker of early-life environment in numerous studies. In our study, we separate the HRS cohort into those born before World War II (prewar, born before 1942) and those born after the start of WWII (postwar, born on or after January 1, 1942). Broadly, our hypothesis that there would be a difference in genetic penetrance of the *APOE* ε4 allele between birth-year cohorts assumes that the later born cohort had a more salubrious early-life environment than did the earlier born cohort. There are many differences in the lived experiences in these two birth-year cohorts. One way that the later born birth-year cohort could have experienced a more health promoting early-life environment is through greater access to education. We were able to test this assumption and the potential that an observed difference in genetic penetrance worked through this difference. While the postwar cohort did have a higher average level of education, this difference did not explain the variation in the relationship between the ε4 allele and cognitive decline between cohorts. Other salient differences may have existed between the cohorts as well. Such differences could include the different disease environments between birth-year cohorts, relative access to health care and food, and access to prenatal care. Other studies have looked at birth-cohort differences in cognitive decline, but the novelty with this particular study is the incorporation of the idea of differential resistance to harm of the *APOE* ε4 allele on such decline.

In contrast to the cohort-wide conceptualization in Aim 2, Aim 3 considers early-life environment at the individual or familiar level via measurement of Adverse Childhood Experiences (ACEs). ACEs are potentially traumatic events that occur in childhood. They are generally fall into three domains: abuse, neglect, and household dysfunction, with subdomains in

each. Individuals who have a history of ACEs are at increased risk for chronic diseases, mental illness and substance abuse.[176,177]

The differences in these conceptualizations contribute to how we might think about the pathways for early-life factors to influence late life outcomes, cognitive outcomes in particular. Glymour and Manly present four types of models for how timing of exposure could related to late life diseases: immediate risk models, cumulative biological models, latency models, and social trajectory models.[3] In immediate risk models, the outcome and the risk factor are temporally proximate to one another and once the risk is mitigated, the risk declines or returns to baseline. This could be the model that the sleep-cognition relationship conforms to in Aim 1; more research is needed to establish such a claim. The remaining three models are germane to our inquiry of early-life environment and late life outcomes. Briefly, cumulative biological models suggest that throughout the life, any period of exposure could inflict biological harm to a functional system that could later increase risk for disease, even if the exposure is not pervasive throughout the lifecourse. Racial and ethnic health disparities may result from racial and ethnic minorities enduring the cumulative effects of adverse social and economic circumstances throughout their lives, a phenomenon termed "weathering" by Geronimus, et al.[178,179] Latency models, or sensitive period models, posit that there are periods through life when developmental changes are occurring and exposure to a risk during these periods could disrupt these normative developments. Barker's fetal origins hypothesis is one such model – proposing that the in-utero period is critical to health and development throughout the lifecourse and that exposures during this time could affect all manner of later life health outcomes including but not limited to cardiovascular disease and neurological diseases.[106,107] Importantly, and to distinguish from the cumulative biological model, in the latency model risk outside of the critical or sensitive period

does not exist. Finally, social trajectory models emphasize the overall amount or duration of an exposure – often an exposure related to socio-economic status or position. These models are similar to cumulative advantage or cumulative disadvantage models and are often applied to health disparities research.[180,181] These four types of models describing timing of exposure are not mutually exclusive and certainly it is likely that they often work simultaneously to produce late life health outcomes.

The cumulative biological model might most aptly apply to our findings in Aim 3 that risk associated with the *APOE* ε4 for cerebrovascular neuropathology was elevated among those in the High ACE class. There is evidence that early-life adversity and trauma alters stress regulatory pathways and subsequent biological functioning, which can lead to dysregulation of the stress response in adulthood and older age.[182,183] Such dysregulation could interact with the known deleterious effect of the *APOE* ε4 allele on cerebrovascular neuropathology to create the added risk observed in postmortem evaluation.

It is also possible that this finding could be situated in a cumulative disadvantage model. There is evidence that ACEs can lead to increased incidence of depression and to behavioral and coping strategies which are themselves risk factors for cardiovascular outcomes such as smoking, alcohol abuse, and compulsive behaviors[145–147]. Further, there is evidence that at least some of these risk factors interact with the *APOE* ε4 allele to increase risk of cardiovascular outcomes cognitive outcomes.[184–186] In Aim 3, there is only suggestive evidence that ACEs interact with the *APOE* ε4 allele to produce worse outcomes with regard to primary AD pathology and we do not observe that ACEs and the *APOE* ε4 allele interact to produce worse cognitive function or trajectories of cognitive decline. The null finding here, among non-cardiovascular outcomes (or possibly non-cardiovascular in the cognitive measures) could lend

evidence to a cumulative disadvantage theory for a stress/inflammation pathway which has been more associated with cardiovascular and cerebrovascular outcomes.

The cumulative disadvantage model could also be applied to the findings of birth-year cohort differences in Aim 2. Indeed, to test whether level of education explains the differential rate of decline attributable to the *APOE* ε4 allele, is to situate a model for the relationship between early-life environment and cognitive decline in this temporal perspective, putting emphasis on the overall amount of education received. In this conceptualization, higher levels of education could also lead to future circumstances such as higher earning and more cognitively stimulating jobs and more resources for healthy lifestyles. These circumstances could promote the development of cognitive reserve – the capacity for the brain to withstand neuropathological accumulation. However, we did not observe that education explained the difference in the association of the *APOE* ε4 allele on cognitive decline between birth-year cohorts. It may be that education is an insufficient measure of possible differences in cumulative advantage across birth-year cohorts when it comes to resilience to the ε4 allele, or it may be that a different pathway explains the variation.

Such a pathway could be via an alternative temporal exposure model, such as the latency model. Under this model, we would presume that there are vital developmental changes happening in the brain during early-life, and that these developmental changes are both directly related to level of education received and are happening up through the periods of life that differentiate these levels (i.e. up through the early 20s). Research by Zahodne, et al., has found that there is evidence for both a cumulative advantage model and a latency model in terms of how level of education itself relates to cognitive decline, but that the applicable model is differentiated by high vs. low educational attainment. They find that the differences in cognitive

decline by educational attainment for those with higher than an 8th grade education are fully mediated by income, pointing to a social trajectory model. Among the low education group, differences in cognitive decline by additional years of education are not mediated by income, suggesting a sensitive period model for the earlier years[124]. In a sensitive period model, a lack of cognitive reserve would not explain differences as it may in a social trajectory model. Instead, impacted subjects would demonstrate a lack of cognitive resistance or brain maintenance – the relative absence of changes in neural resources. We could also situate the null findings of Aim 3 in a latency model, and interpret our findings to mean that if the early childhood is a period of brain development with the potential to be impacted by events which could later manifest as limited resistance to the *APOE* risk allele, ACEs are not events that effect the brain itself during this sensitive period. In other words, we may conclude that the particular brain reserve that might develop against genetic risk for cognitive decline are not necessarily set in motion to fail because of early childhood adversity. However, we must also consider this finding alongside the finding that ACEs were related to significantly lower average cognitive function. And while they were not related to decline as we might expect with the High ACE class had a slower rate of decline relative to the EN-Mid class, such an observation could be attributed to the older age of the Rush cohort, and the possibility that the High ACE group began their trajectory of decline much earlier in their lives, and then the decline was more gradual. That ACEs are related to worse cognitive outcomes, irrespective of *APOE* ε4 status, could speak to the possibility that the detrimental effect of experiencing ACEs early in life impacts cognition and cognitive trajectories earlier in life such that when the genetic risk for decline becomes salient, the damage has already been done, so to speak.

A latency model may aptly apply to the birth-year cohort findings in Aim 2. This would stress the timing of exposure and may speak to different disease and/or nutritional environments between the birth-year cohorts.

Finally, turning to the results of the neuropathology models, we see suggestive evidence in the primary AD models that there is variation in the relationship of the ε4 allele to pathology by ACE class. But this could be due to the higher prevalence of pathology in the ε4 group, the capacity to detect smaller risk associations in such a population. More intriguing is the modification of the association of the ε4 allele to cardio pathology outcomes by ACE class, with the High ACE class having higher risk, contrasted with the main effects model where the EN-Mid group had a higher risk. Emotional neglect has been associated with chronic gross infarcts in the Rush cohorts, so the main effects model is consistent with that literature. It is possible that the High ACE group also has higher lifetime and general levels of stress, contributing to an inflammation/cardiovascular pathway that would diminish resistance to the added insult of the possession of an ε4 allele. There is evidence that individuals that report high levels of ACEs, broadly, are more likely to have neuroticism as personality type which itself is more highly associated with cardiovascular health outcomes.[173–175]

Aside from the clear difference in the conceptualization of early-life environment, there are other differences between these studies that may explain a difference in findings. First, these cohorts, while both studies of older adults, are composed of differing samples of that population. The HRS cohort is a nationally representative sample and this particular analysis includes ages from 50 to 75, with an average age of 68. The MAP is a sample of individuals in and around the Chicago area, many of whom live in senior housing communities, with an average age of 78. In the HRS cohort, starting at a younger age and limiting the analysis to age 75 means that we may

not observe the most severe cognitive decline, generally occurring after our cut-off. However, in the HRS cohort, we do observe differences between the cohorts in the decline models, whereas we do not in Rush. This could be because the early-life exposure in Rush impacts cognitive decline earlier in life than the differences between the birth-year cohorts in HRS.

Second, the potential selection bias in the HRS cohort with regard to the composition of the genetic sample cannot be understated. Subjects in the HRS study had to survive until 2006 in order to contribute to the genetic sample, a criterion which meant that many more of the prewar birth-year cohort were not able to participate compared to the postwar birth-year cohort. Further, survival until 2006 in the prewar birth-year cohort is strongly associated with overall health, cognitive function, and level of education. The MAP cohort, on the other hand, does not suffer from this potential bias as genotyping was performed on a higher proportion of subjects and it is not as correlated with the measure of early-life environment. However, the MAP cohort was recruited at a much older age, compared to HRS. The average age of enrollment in MAP was 76 years old, which likely introduced selection bias into the overall study. It is possible that both potential exposures, possession of an *APOE* ε4 allele and history of ACEs, would be associated with survival and/or participation in the MAP. Such underrepresentation could lead to an underestimation of a potential association between the exposures and the outcome of cognitive decline.

Finally, the measure of cognitive function itself is very different across studies. The HRS uses a validated measure of global cognitive function, the TICS. The MAP, however, uses a multidimensional assessment of cognitive function comprised of 19 neuropsychological tests. It is much more sensitive to changes in cognition and allowed us to look at domain specific cognitive decline.

These studies consider the potential modification of the *APOE* ε4 allele by early-life environment, conceptualized in two very different ways. The disparate findings across studies speak to the importance of the definition of early-life environment, the population under investigation, and the potential pathways that we think about when considering lifecourse models of cognitive aging.

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