

THE IMPACT OF INTERACTIONS BETWEEN APOE GENOTYPE AND SELF-REPORTED
SLEEP QUALITY ON COGNITIVE AGING

By

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ABSTRACT

Previous research has found that cognitive functioning in advanced age can be impacted both by genetic and behavioral factors. This study sought to look at the effects of apolipoprotein E (APOE) genotype, self-reported sleep quality, and age on measures of cognitive functioning. A cohort of healthy older adults (50-89 years old) was split into older and younger age groups for analysis in relation to sleep quality and APOE ϵ 4 carrier status. A three-way ANCOVA was performed to test main effects and interactions. Significant main effects were observed for age across all measured cognitive domains, with older age predicting worse scores. No significant two-way interactions were found. Significant three-way interactions between APOE genotype, sleep quality, and age were observed for processing speed, executive function, and memory. Follow-up testing suggests that among non APOE ϵ 4 carriers, poor sleep may lead participants to be more susceptible to the effects of older age. APOE ϵ 4 carrier status appeared to exacerbate the negative effects of poor sleep among the younger group, as well as the effect of age for good sleepers. A deeper understanding of the relationship between APOE genotype, sleep quality, and age could lead to interventions to reduce the risk of developing dementia among older adults.

INTRODUCTION

As many as 5.4 million Americans are currently living with Alzheimer's disease (AD). This number is expected to climb as high as 14 million by 2050. The cost to society of AD and other dementias is extremely high, with more than 15 million individuals providing unpaid care to an afflicted loved one, and the nation spending an estimated \$259 billion on these conditions in 2017 alone (Alzheimer's Association, 2017). The causes of AD are not yet well understood and are the subject of much research. There have, however, been some breakthroughs in recent years regarding the genetic and behavioral traits that put an individual at heightened risk of developing these conditions as they age. Two factors that have been identified as potential risk factors for poor cognitive aging are carrying the $\epsilon 4$ allele of the apolipoprotein E gene and poor sleep quality. Evidence has shown that these factors can produce significant effects on cognitive functioning even in individuals who are not diagnosable with dementia. An improved understanding of the interaction between these risk factors, particularly in relation to age, could provide valuable insights for future prevention and mitigation of cognitive decline and dementia.

Age-Related Cognitive Decline

Subtle declines in cognitive functioning are typically considered normal in older age. However, when these declines begin to significantly impair two or more cognitive domains in a person's everyday life, they are considered to be suffering from dementia (Lezak et al., 2004). Although there are many subsets of dementia, by far the most prevalent are AD and vascular dementia. Vascular dementia is typically precipitated by a specific event such as a stroke, causing a rapid, sharp decline in cognition that can occur from one day to the next. In contrast, AD tends to progress more slowly and is more difficult to attribute to a specific cause. Current

research is largely focusing on the interaction between genetic factors and health/lifestyle factors (National Institute on Aging, 2017). Particular attention is being paid to health behaviors that can minimize a person's risk for developing dementia, such as diet and exercise.

Even when dementia is not diagnosable, normal aging brings with it declines in many different domains of cognition. Processing speed, executive function, and memory are all subject to diminishing efficiency. Even higher order processes, such as language, are thought to experience normal decay with increasing age (Glisky, 2007). Age-related declines in fine motor movement have also been documented extensively (Krampe, 2002).

Sleep Quality and Aging

Sleep quality has a negative correlation with increasing age. As the body ages, slow wave sleep decreases, as does sleep efficiency. Complaints about poor sleep rise significantly with age (Leger et al., 2000). Sleep onset latency (i.e. amount of time taken to fall asleep) has been shown to increase with age, and--once asleep--older adults are more likely to be awakened by external stimuli. Overall sleep duration shortens and becomes more fragmented as nighttime awakenings occur more frequently (Mander et al., 2017). Daytime sleepiness is also impacted by aging, with Foley et al. (2007) finding that a quarter of older adults regularly change or cancel their daytime plans because of sleepiness. It is not entirely clear what is responsible for these changes in sleep quality. However, older age has been tied to a decrease in both the amplitude and density of slow waves (Dube et al., 2015), as well as a reduction in neurons that promote wakefulness (Hunt et al. 2015).

Sleep Quality and Cognitive Function

Poor quality sleep has been linked to a higher risk for the development of dementia and AD (National Sleep Foundation, 2017). Elderly adults with poor self-reported sleep quality were found to score significantly lower on the Mini-Mental State Exam (MMSE) and have higher rates of dementia (Jirong et al., 2012). Initial memory encoding has been shown to be negatively impacted by poor sleep quality, although these results were only found when looking at objective rather than subjective measures of sleep quality (Lo et al., 2016). Sleep-dependent memory consolidation is also diminished in advanced age (Spencer et al., 2007). Executive function is another cognitive domain that exhibits significant declines among older poor sleepers (Lo et al., 2016). Decreased sleep has also been shown to have a negative effect on motor skills (Forest & Godbout, 2000).

The exact reason why sleep quality has such a strong relationship with cognitive functioning is not well understood, but one potential explanation is the observed correlation between poor sleep quality and the accumulation of the β -amyloid molecule, which is linked to cognitive decline and AD. Higher levels of β -amyloid can be indicative of preclinical AD, meaning that individuals who do not yet display clinical symptoms of AD may already be being impacted by amyloid deposition in subtle ways. For example, Ju et al. found that individuals whose spinal fluid showed higher amounts of β -amyloid displayed poorer sleep quality than individuals who did not have amyloid buildup. Interestingly, they found that only sleep quality, not quantity was affected (Ju et al., 2013).

Similarly, in a study of older women (mean age 83.5 years) Blackwell et al. (2006) found that those with lower sleep efficiency exhibit a higher risk for cognitive impairment. They also reported that cognitive ability has a negative correlation with both number of daily naps and sleep latency. Individuals afflicted with mild/moderate AD showed greater daytime sleepiness

than their healthy counterparts. Those with moderate AD displayed significantly greater sleepiness when compared to both the control group and the mild AD group, and the mild AD group was significantly sleepier than the control group.

There have, however, also been some studies published that suggest that older individuals are actually less susceptible to the negative effects of diminished sleep quality than younger individuals. Phillip et al. (2004) tested vigilance in 20-25 year olds and in 52-63 year olds after 24 hours of sleep deprivation and found that the lack of sleep only impacted vigilance within the younger group. A similar study found that after only getting 4 hours of sleep for 3 consecutive nights, older participants were able to maintain their performance level on a psychomotor vigilance task better than younger subjects (Stenuit & Kerkhofs, 2005). However, Glisky (2007) noted that these effects may be observable because older participants have become adept at using various strategies to mask cognitive or motor declines they might be experiencing.

APOE Genotype and Cognitive Functions

Apolipoprotein E (APOE) is a gene that has three variants: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. Since there are two alleles for every gene, there are 6 different combinations possible. Worldwide, the frequency of the $\epsilon 4$ allele is 13.7%. However, 40% of AD patients have the $\epsilon 4$ variant (Liu, 2013). An individual who is homozygous for the $\epsilon 4$ allele has a 91% chance of developing AD in their lifetime, with a standard onset age of 68. This is compared to $\epsilon 4$ heterozygotes and non-carriers, who only have a 47% and a 20% chance of having AD respectively. Heterozygotes for the $\epsilon 4$ allele had a mean onset age of 76 years, while non-carriers typically did not develop the disease until age 84 (Liu, 2013).

Apolipoprotein E is a cholesterol carrier and is involved in the brain's lipid transport. These proteins bind to receptors on cells to bring lipids to the cells. They are also capable of binding to β -amyloid, which is thought to be a contributing factor to the degeneration associated with AD. The relationship between β -amyloid deposition and cognition has been shown to be modified by APOE carrier status, with APOE ϵ 4 carriers experiencing greater cognitive declines in relation to how much β -amyloid is present (Kantarci et al., 2012). The importance of the function performed by the APOE gene has led to its involvement in more than just AD. The APOE ϵ 4 allele has been implicated as a risk factor for a wide variety of neurodegenerative diseases, including Multiple Sclerosis and Parkinsonian dementia (Leduc, 2011).

The Apolipoprotein E gene is thought to interact with environmental and behavioral factors to determine the degree of risk to an individual for developing AD or other forms of dementia (Alzheimer's Association, 2017). APOE genotype has been shown to have effects on cognitive domains including memory, executive function, and language, with APOE ϵ 4 carriers experiencing worse cognitive outcomes (Caselli et al., 2009; Raichlen & Alexander, 2014; Kantarci et al., 2012).

Sleep Quality and APOE Genotype Interactions

The interaction between sleep quality and APOE ϵ 4 carrier status has been the topic of several recent research studies. Findings suggest that even among cognitively normal subjects, having an APOE ϵ 4 genotype is correlated with poorer overall sleep quality. For example, higher numbers of nighttime awakenings were reported by carriers compared to non-carriers (Kahya et al., 2017). Interestingly, findings suggest that carriers often do not self-report worse overall sleep

quality, even when their sleep is objectively found to be significantly poorer than that of non-carriers (Drogos et al., 2016).

Sleep Quality, APOE Genotype, and Age Interactions

The interactions between sleep quality, APOE genotype, and age are not yet well understood. Lim et al. (2013) found that sleep modifies the risk of APOE ϵ 4 carriers developing AD. APOE ϵ 4 carriers who suffer from poor quality sleep caused by sleep apnea or hypopnea have been shown to exhibit increased memory problems (O'Hara et al., 2005). A significant interaction between APOE genotype and slow wave sleep on cognitive abilities has been observed among older adults, with APOE ϵ 4 homozygotes spending a longer amount of time in slow wave sleep and exhibiting worse cognitive functioning as measured by the MMSE. This result is surprising as a decrease in cognition is typically associated with a decline in slow wave sleep. However, current theories suggest that this result may be due to the synaptic pruning that occurs during slow wave sleep, which may be overactive in these older ϵ 4 homozygotes (Tranah et al., 2018).

Objective of the Current Project

The primary focus of this research is to ascertain whether a cohort of cognitively normal, community-dwelling adults between the ages of 50 and 89 show evidence of an interaction between age, APOE ϵ 4 carrier status, and self-reported quality of sleep when tested on measures of cognitive aging including memory, executive functioning, processing speed, language, and motor speed.

I hypothesize that older participants will perform more poorly than their younger counterparts across all cognitive domains. I also hypothesize that APOE ϵ 4 carriers will perform worse than non-carriers on cognitive tests related to memory and executive function. I further hypothesize that poor sleepers will underperform compared to better sleepers, specifically on measures of memory, executive function, and motor speed.

Additionally, I hypothesize that there will be a significant two-way interaction observed between APOE genotype and sleep quality across several cognitive domains, with the most pronounced effect predicted for measures of memory. I predict that the combined effect of APOE ϵ 4 carrier status and sleep quality will be greater than the effect of either one by itself, and that participants who are ϵ 4 carriers and exhibit poor sleep quality will perform worse than those who are non-carriers or report good sleep quality. It is also hypothesized that two-way interactions will be observed for age and APOE genotype as well as age and sleep quality measures. I predict that memory will be the cognitive domain showing a significant interaction, with the risk factors of APOE ϵ 4 carrier status and poor sleep moderating the effect of age.

The central hypothesis is that there will be evidence for a three-way interaction between age, APOE genotype and sleep quality. Specifically, it is hypothesized that those individuals who are within the older age group, are classified as “poor sleepers” and are also carriers of the APOE ϵ 4 allele will have the worst outcomes on cognitive measures effected by aging, including memory, executive function, and processing speed.

METHODS

Participants

A sample of 200 participants, 50-89 years of age, were drawn from a cohort of 220 neurologically healthy older adults who had been part of a longitudinal study on healthy cognitive aging. The 20 participants who were excluded from the current study had missing or incomplete data. All participants received medical, neurological, and psychiatric screening to rule out any significant disorders that could affect cognitive performance. Potential participants were excluded if they received a Mini Mental State Examination (MMSE) score < 26 (Folstein et al., 1975). A median split by age was performed to divide the group into an “older” and a “younger” group. A Pearson chi square test showed that there was no significant gender difference between the older and younger groups [$\chi^2(1)=0.020$, $p=0.887$], but the groups did differ for self-reported hypertension status [$\chi^2(1)=6.395$, $p=0.011$]. T-tests showed that the groups did not significantly differ on years of education [$t(198)=1.479$, $p=0.141$] or Geriatric Depression Scale score [$t(197)=0.541$, $p=0.589$]. The groups did differ significantly for the total number of years spent as a smoker [$t(196)=-2.828$, $p=0.005$], and a small but significant difference was observed for MMSE scores [$t(198)=4.618$, $p=0.00007$]. Participant characteristics are shown in Table 1.

APOE Genotyping

APOE genotype was determined by analyzing blood samples given by the participants. DNA was amplified using a polymerase chain reaction, digested by the HhaI restriction isotyping enzyme, and autoradiographed (Alexander et al., 2012). Participants were classified as either APOE $\epsilon 4$ carriers or non-carriers depending on whether they were found to have at least one copy of the $\epsilon 4$ allele or not.

Pittsburgh Sleep Quality Index

Participant's sleep quality was classified as either "good" or "poor" based on their global score on the Pittsburgh Sleep Quality Index (PSQI). Global PSQI scores range from 0 to 21, with higher scores indicating poorer sleep quality based on metrics such as total sleep time, sleep latency, frequency of nighttime awakenings, and self-reported sleep quality. "Poor" sleep is denoted by a global PSQI score of 6 or greater. A score of 6 or higher illustrates that a participant has "severe difficulties in at least two areas, or moderate difficulties in more than three areas" of the sleep components measured by the PSQI (Buysse et al., 1989). Individuals who had been diagnosed with sleep apnea were excluded from the study as prior research has indicated that sleep apnea can have a severe impact on cognitive functioning by causing hypoxia and systemic inflammation (Lal et al., 2012).

Neuropsychological Testing

Participants in the study underwent a series of neuropsychological tests aimed at gathering an accurate picture of their cognitive abilities. Of particular interest to this current study are the tests that measured memory, executive function, processing speed, language ability, and motor speed.

Memory was assessed using four subtests of the Buschke Selective Reminding Test (BSRT; Buschke, 1973). For this measure, participants are read a list of words and then tested on their recall at multiple time points. For the current study, Total Recall, Long Term Recall (LTR), Consistent Long Term Recall (CLTR), and Delayed Recall after 30 minutes were the measures used for analysis.

Executive function was also tested with three neuropsychological tests: Trail Making Test part B (TMT B; Reitan, 1958), Stroop Color Word Interference (Stroop Interference; Stroop, 1935), and WAIS-IV Digit Span (WAIS-IV DS; Wechsler, 2008). TMT B requires participants to draw lines connecting both randomly placed numbers and letters in ascending and alphabetical order, alternating between the two. The classic Stroop Interference task presents examinees with names of colors that are printed in a different color font than the color name that is written (for example: the word “red” written in green font). Examinees are asked to inhibit their response of wanting to read the word that is printed and instead say only the font color. The WAIS-IV DS test has three parts: the first one involves the participants trying to repeat sequences of digits back exactly as they heard them, the second one asks them to repeat back similar sequences but backwards, and the third one involves repeating the digit sequence back in ascending order.

Processing Speed was measured by Trail Making Test part A (TMT A; Reitan, 1958), and two tests that are included in the Wechsler Adult Intelligence Scale IV: Coding and Symbol Search (WAIS-IV CD, WAIS-IV SS; Wechsler, 2008). TMT A measures processing speed by having participants draw lines connecting printed numbers on a page in ascending order as quickly as they can. WAIS-IV CD requires participants to “code” a series of numbers with specific symbols using a key. The WAIS-IV SS test has examinees scan to see if they can find symbols on a page that match a given target symbol. Both of the WAIS-IV subtests have imposed time limits so that a participant’s processing speed can be determined.

Language was measured by two tests: the Boston Naming Test (BNT; Kaplan, 1983), which asks participants to provide the names for a series of objects presented with line drawings,

and the Category Fluency Test (Rosen, 1980), which has participants list as many items that belong to a certain category as they can within a limited amount of time.

Motor speed was indicated by performance on the dominant and non-dominant hand versions of two separate tasks: the Finger Tapping Test (FTT; Reitan & Wolfson, 1993) and the Grooved Pegboard Test (GPT; Lafayette Instrument, 2002). The FTT has participants tap the index finger for each hand for a specified amount of time to record their fine motor speed. The GPT has a lock and key design in which pegs must be rotated in order to fit into their corresponding slots on a grid.

Procedure

Data for this study was taken from the Brain Aging and Memory Study (BAMS). Potential BAMS participants were first screened over the phone to exclude individuals with confounding conditions such as depression or dementia. Participants who were deemed eligible were then asked to provide a blood sample for genetic testing as well as completing demographic and family history questionnaires. Participants came in for a separate visit to complete the neuropsychological battery detailed above. For the current study, participants were placed into groups based on age, APOE ϵ 4 carrier status, and sleep quality. A median split was performed for age (median = 69.97 years). Participants with ages under the median are classified as the “younger” group, while those over the median are referred to as the “older” group. Those participants whose blood work indicated that they had at least one APOE ϵ 4 allele are referred to as “carriers”, while their counterparts are the “non-carrier” group. Participants who scored a 6 or higher on the global PSQI measure have been classified as “poor” sleepers. Participants who had a global PSQI score of 5 or under are hereafter referred to as “good” sleepers. Of the initial

cohort, 20 individuals were excluded from analysis because they were missing either APOE genotype or PSQI data.

Statistical Analyses

A three-way Analysis of Covariance (ANCOVA) was performed with age, APOE carrier status, and sleep quality as the independent variables. Education level, gender, self-reported hypertension status, years spent as a smoker, and score on the Geriatric Depression Scale were included as covariates. Main effects, two-way interactions and three-way interactions were analyzed for all 16 of the neuropsychological tests detailed above. An alpha level of $p < 0.05$ was used to determine statistical significance. Significant interaction results were followed up with pairwise t-tests to determine the existence of any simple effects. All statistical analyses were done using SPSS (Windows version 18, Chicago, IL, USA).

Table 1

Variables	Older Group M (SD)	Younger Group M (SD)	p-value
Age, yrs.	78.9 (5.1)	60.8 (5.4)	
Education, yrs.	15.8 (2.6)	16.3 (2.4)	0.141
Sex (M/F)	51/49	52/48	0.887
Hypertension (Y/N)	43/57	26/74	0.011
GDS	1.0 (1.5)	1.1 (1.9)	0.589
Years Smoked	11.2 (16.8)	5.6 (10.1)	0.005
MMSE	28.6 (1.4)	29.4 (0.9)	0.00007

Table 1: Means and standard deviations for younger and older age group. GDS stands for Geriatric Depression Scale and MMSE stands for Mini-Mental State Examination. P-values for years of education, GDS, years smoked, and MMSE were found using t-tests; frequency p-values (sex and hypertension status) were found using a chi square test.

RESULTS

Main Effects of APOE Genotype, Sleep Quality, and Age

Significant main effects were observed only for age group after controlling for education level, gender, self-reported hypertension status, years spent smoking, and depression (as measured by the Geriatric Depression Scale). These main effects between the younger and older age groups were statistically significant [$F(1, 184) \geq 4.084, p \leq 0.047$] for all 16 neuropsychological tests except BSRT Delayed Recall, which showed a trend toward an age effect (Table 4). The older group performed worse than the younger group on each test that had a significant main effect for age, as well as on the test that indicated a trend towards an age effect. There were no significant main effects for APOE genotype and sleep quality.

Two-Way Interactions between APOE Genotype, Sleep Quality, and Age

There were no significant two-way interactions observed between APOE genotype and sleep quality, APOE genotype and age, or sleep quality and age for any of the 16 measures of cognitive functioning. However, there was a possible trend observed among some of the motor speed tasks when looking at interactions between both APOE genotype and age as well as sleep quality and age.

The test for an interaction between APOE carrier status and age showed trends for both an APOE x Age interaction on the dominant hand part of the Grooved Pegboard Test [$F(1,183)=2.925, p=0.089$] and an interaction on the non-dominant hand part of Grooved Pegboard Test [$F(1,182)=3.717, p=0.055$]. Exploratory follow-up pairwise tests showed significant simple effects for both age and APOE genotype. For the dominant hand part of the GPT, age had a significant effect both among non-carriers [$F(1,132)=56.98, p=0.851 \text{ E-}19$] and

among carriers [$F(1,60)=13.04$, $p=0.00002$]. In both groups, the younger group scored significantly better than the older group. There was also a surprising significant effect for APOE carrier status within the older age group [$F(1,96)=5.22$, $p=0.025$], with APOE $\epsilon 4$ carriers outperforming the non-carriers. No significant effect for APOE genotype was observed within the younger group [$F(1,96)=0.82$, $p=0.443$]. For the non-dominant hand portion of the GPT, a significant age effect was again observed within non-carriers [$F(1,132)=46.78$, $p=0.217$ E-10] and carriers [$F(1,60)=9.13$, $p=0.005$]. Similarly to the results of the dominant hand part of the GPT, the older group scored worse than the younger group on this part of the GPT as well. A trend was observed for APOE carrier status among the older cohort [$F(1,96)=2.55$, $p=0.091$], with carriers again outperforming non-carriers. APOE genotype did not have a significant effect among the younger participants [$F(1,96)=0.73$, $p=0.489$].

Similarly, trends towards an interaction between sleep quality and age were seen for the dominant hand part of the Finger Tapping Test [$F(1,182)=3.371$, $p=0.068$] and the dominant hand part of the Grooved Pegboard Test [$F(1,183)=3.759$, $p=0.054$]. Exploratory follow-up tests showed significant simple effects. On the dominant hand part of the FTT, a significant effect was seen for age among those with good sleep quality [$F(1,135)=39.20$, $p=0.177$ E-7], with older chronological age predicting worse performance. Among those with poor sleep quality, age did not have a significant effect [$F(1,57)=2.64$, $p=0.124$]. A trend was observed for sleep quality within the younger group [$F(1,96)=2.77$, $p=0.098$], where better sleep quality tended to be associated with a higher average score. No significant effect of sleep quality was observed within the poor sleep quality group [$F(1,57)=0.46$, $p=0.637$]. For the dominant hand portion of the GPT, age had a significant effect for both the good sleeper and poor sleeper groups. Among good sleepers, older age predicted worse performance [$F(1,135)=30.71$, $p=0.649$ E-12], and the same

relationship was observed among poor sleepers [$F(1,57)=32.92$, $p=0.126 \times 10^{-11}$]. A significant effect of sleep quality was observed among the older group [$F(1,96)=4.72$, $p=0.036$], with poor sleepers scoring significantly worse than good sleepers. Sleep quality did not have a significant effect on performance among the younger group [$F(1,96)=0.87$, $p=0.268$].

Three-Way Interactions between APOE Genotype, Sleep Quality, and Age

Significant three-way interactions between APOE genotype, sleep quality, and age were observed for BSRT CLTR [$F(1,183)=4.636$, $p = 0.033$], Trail Making Test part B [$F(1,183)=5.458$, $p = 0.021$], and Trail Making Test part A [$F(1,184)=8.356$, $p = 0.004$] (Table 4).

The BSRT CLTR showed significant simple effects when pairwise tests were performed (Figure 1). Among non-carriers who reported good sleep quality, age had a significant effect [$F(1,183)=14.928$, $p=0.0002$] with the younger group outperforming the older group. Age also had a significant effect for non-carriers who had poor sleep quality [$F(1,183)=11.445$), $p=0.001$]. In this group, younger participants again did better on the test than their older counterparts. Among carriers with good sleep quality, age again predicted the BSRT CLTR score [$F(1,183)=25.002$), $p=0.000001$], with a higher chronological age being associated with a worse score. Age did not significantly predict performance among carriers with poor sleep quality [$F(1,183)=0.353$, $p=0.553$]. There were no significant effects observed between any of the groups on BSRT CLTR performance for APOE carrier status ($p \geq 0.129$) or for sleep quality ($p \geq 0.111$).

Statistically significant effects were also observed for age on TMT B (Figure 2). Among non-carriers with poor sleep quality, the older group scored significantly worse than the younger

group [$F(1,183)=10.189$, $p=0.002$] and the same difference was observed among carriers with good sleep quality [$F(1,183)=10.466$, $p=0.001$]. Effects of age for non-carriers with good sleep quality and carriers with poor sleep quality were not statistically significant ($[F(1,183)=0.793$, $p=0.374$] and [$F(1,183)=0.214$, $p=0.644$], respectively). APOE carrier status had a significant effect within the older participants who had good sleep quality [$F(1,183)=6.319$, $p=0.013$]. Within this group, APOE $\epsilon 4$ carriers took significantly longer to complete the task than non-carriers. APOE carrier status did not have a significant effect within the older poor sleeper group or among younger participants, regardless of sleep quality ($p \geq 0.320$). For older non-carriers, there was also a trend observed for the measure of sleep quality, with poor sleep quality predicting worse performance on the task [$F(1,183)=3.130$, $p=0.079$]. For the other groups (younger non-carriers, older carriers, and younger carriers) there was no significant effect or trend observable ($p \geq 0.125$).

For TMT A (Figure 3), age had a significant effect within both non-carrier poor sleepers [$F(1,184)=11.755$, $p=0.001$] and carrier good sleepers [$F(1,184)=9.462$, $p=0.002$]. For both of these groups, the older group performed significantly worse than their younger counterparts. No significant effect was seen for age within the non-carrier good sleepers or the carrier poor sleepers groups ($[F(1,184)=1.513$, $p=0.220$] and [$F(1,184)=0.173$, $p=0.678$], respectively). APOE genotype also had a significant effect among younger poor sleepers [$F(1,184)=4.213$, $p=0.042$], with carriers performing worse than non-carriers. A trend was also observed for older good sleepers regarding APOE genotype [$F(1,184)=3.862$, $p=0.051$], with carriers again taking longer to complete the task than non-carriers. No significant effects or trends were observed among younger participants with good sleep quality or older participants with poor sleep quality ($p \geq 0.272$). A possible trend with regards to sleep quality was observed among the younger non-

carrier group [$F(1,184)=2.813, p=0.095$]. Within this sample, those individuals with better sleep quality surprisingly performed worse than those with poor sleep quality. No significant effects or trends were observed for sleep quality in any of the other groups ($p \geq 0.124$).

Table 2

	APOE ε4 Carrier Status		Sleep Quality		Age	
	Non-Carriers	Carriers	Good Sleepers	Poor Sleepers	Younger	Older
<i>n</i>	136	64	139	61	100	100
Memory						
<i>BSRT Total</i>	103.9 (19.5)	103.6 (22.3)	105.8 (20.6)	99.4 (19.3)	112.8 (16.4)	94.7 (20.0)
<i>BSRT LTR</i>	84.9 (29.5)	85.2 (33.5)	87.8 (30.8)	78.7 (29.9)	97.3 (26.1)	72.6 (30.1)
<i>BSRT CLTR</i>	61.8 (36.1)	63.3 (39.2)	66.0 (37.8)	54.0 (34.1)	78.3 (33.3)	46.2 (33.7)
<i>BSRT Delay</i>	8.1 (2.7)	8.0 (2.9)	8.1 (2.8)	7.9 (2.5)	8.7 (2.5)	7.4 (2.7)
Executive Function						
<i>TMT B</i>	76.5 (31.3)	81.6 (41.3)	76.2 (34.4)	82.5 (35.5)	67.3 (26.9)	89.0 (38.4)
<i>Stroop CW</i>	37.1 (9.5)	35.8 (9.2)	36.7 (9.5)	36.5 (9.4)	40.7 (8.4)	32.6 (8.6)
<i>WAISIV DS</i>	27.5 (4.8)	27.3 (5.1)	27.4 (4.9)	27.4 (4.9)	28.3 (5.1)	26.5 (4.6)
Processing Speed						
<i>TMT A</i>	32.9 (11.9)	34.6 (13.6)	32.9 (12.8)	34.7 (11.8)	29.6 (10.5)	37.3 (13.1)
<i>WAISIV CD</i>	61.7 (14.8)	59.2 (13.8)	61.1 (14.8)	60.5 (14.0)	66.9 (14.5)	54.9 (11.8)
<i>WAISIV SS</i>	28.4 (7.1)	26.9 (8.4)	28.8 (7.7)	25.8 (6.8)	31.2 (6.3)	24.5 (7.2)
Language						
<i>Category Fluency</i>	20.9 (5.2)	20.0 (6.3)	20.7 (5.6)	20.4 (5.5)	22.4 (5.2)	18.8 (5.4)
<i>BNT</i>	56.7 (3.5)	56.7 (3.4)	57.0 (3.3)	56.1 (3.6)	57.5 (2.7)	56.0 (3.9)
Motor Speed						
<i>FTT DH</i>	41.7 (8.1)	40.4 (9.8)	42.0 (9.3)	39.7 (7.2)	44.1 (7.2)	38.4 (9.2)
<i>FTT NDH</i>	39.4 (9.0)	36.6 (7.5)	38.3 (8.2)	38.7 (9.6)	40.9 (7.8)	36.1 (8.8)
<i>GPT DH</i>	94.0 (26.4)	92.2 (27.2)	90.4 (24.0)	100.2 (31.0)	76.7 (13.9)	110.4 (25.7)
<i>GPT NDH</i>	102.5 (34.7)	100.8 (32.5)	99.9 (33.2)	106.6 (35.2)	85.0 (20.9)	119.1 (35.9)

Table 2: Means and Standard Deviations for scores on all 16 neuropsychological tests broken down between APOE ε4 non-carriers and carriers, good sleepers and poor sleepers, and the younger group and the older group. BSRT Total = Buschke Selective Reminding Test, Total Recall; BSRT LTR = Buschke Selective Reminding Test, Long Term Recall; BSRT CLTR = Buschke Selective Reminding Test, Consistent Long Term Recall; BSRT Delay = Buschke Selective Reminding Test, Delayed Recall; TMT B = Trail Making Test part B; Stroop CW = Stroop Color Word Interference; WAISIV DS = Wechsler Adult Intelligence Scale IV, Digit Span; TMT A = Trail Making Test part A; WAISIV CD = Wechsler Adult Intelligence Scale IV, Coding; WAISIV SS = Wechsler Adult Intelligence Scale IV, Symbol Search; BNT = Boston Naming Test; FTT DH = Finger Tapping Test, Dominant Hand; FTT NDH = Finger Tapping Test, Non-Dominant Hand; GPT DH = Grooved Pegboard Test, Dominant Hand; GPT NDH = Grooved Pegboard Test, Non-Dominant Hand.

Table 3

	Younger Group				Older Group			
	Non-Carriers		Carriers		Non-Carriers		Carriers	
	Good Sleep	Poor Sleep	Good Sleep	Poor Sleep	Good Sleep	Poor Sleep	Good Sleep	Poor Sleep
<i>n</i>	55	15	22	8	37	29	25	9
Memory								
<i>BSRT Total</i>	113.1 (16.0)	109.9 (11.3)	116.9 (16.9)	105.5 (24.0)	96.6 (21.1)	92.5 (17.8)	93.0 (20.5)	98.4 (23.1)
<i>BSRT LTR</i>	97.2 (26.0)	92.7 (19.8)	103.7 (27.1)	88.8 (34.5)	75.7 (31.0)	69.0 (27.6)	70.4 (29.6)	77.4 (38.9)
<i>BSRT CLTR</i>	77.7 (32.7)	72.7 (26.9)	88.7 (34.5)	63.6 (41.8)	50.2 (37.9)	40.5 (28.7)	42.9 (30.2)	57.4 (40.0)
<i>BSRT Delay</i>	8.9 (2.6)	8.4 (1.6)	8.8 (2.7)	8.3 (3.3)	7.3 (2.9)	7.5 (2.5)	7.2 (2.8)	8.3 (2.7)
Executive Function								
<i>TMT B</i>	69.1 (27.7)	61.5 (17.7)	64.6 (23.5)	73.8 (43.0)	79.1 (27.9)	95.1 (38.7)	98.9 (52.3)	84.3 (23.9)
<i>Stroop CW</i>	39.9 (9.6)	43.5 (7.1)	41.3 (6.3)	38.6 (7.7)	33.1 (6.9)	33.3 (10.0)	30.9 (10.2)	33.1 (5.2)
<i>WAISIV DS</i>	27.9 (4.9)	29.4 (6.1)	28.8 (5.5)	28.1 (3.1)	26.7 (4.1)	26.7 (4.6)	26.2 (5.4)	25.8 (4.5)
Processing Speed								
<i>TMT A</i>	30.4 (12.1)	25.9 (3.7)	28.1 (7.3)	35.4 (13.6)	34.6 (11.0)	39.0 (12.7)	40.1 (17.0)	34.6 (8.9)
<i>WAISIV CD</i>	66.1 (15.9)	73.4 (12.0)	65.6 (11.1)	63.0 (15.7)	55.6 (10.8)	54.8 (11.6)	53.7 (14.7)	55.1 (7.7)
<i>WAISIV SS</i>	31.8 (6.9)	31.3 (4.9)	30.8 (5.7)	28.6 (6.7)	26.2 (5.7)	23.2 (5.9)	24.2 (10.0)	22.9 (6.7)
Language								
<i>Category Fluency</i>	22.6 (5.0)	23.7 (3.5)	21.3 (5.2)	21.4 (8.2)	19.0 (5.3)	18.7 (4.3)	18.4 (6.4)	19.8 (6.8)
<i>BNT</i>	57.8 (2.7)	57.1 (2.6)	57.0 (3.2)	57.6 (1.5)	56.5 (3.4)	54.9 (4.6)	56.1 (4.4)	56.9 (1.6)
Motor Speed								
<i>FTT DH</i>	45.2 (7.3)	42.5 (7.4)	43.6 (7.5)	41.2 (5.6)	39.2 (8.3)	37.7 (7.3)	37.4 (12.7)	40.0 (7.1)
<i>FTT NDH</i>	41.7 (7.4)	41.9 (10.2)	39.1 (7.5)	38.7 (6.2)	36.3 (8.1)	37.6 (10.9)	33.5 (7.9)	37.1 (5.2)
<i>GPT DH</i>	76.9 (13.9)	73.9 (9.6)	79.2 (16.5)	74.4 (13.9)	109.7 (19.9)	118.2 (26.9)	102.5 (28.0)	110.8 (33.1)
<i>GPT NDH</i>	85.4 (23.6)	79.9 (12.2)	87.2 (17.5)	85.5 (24.8)	118.2 (35.3)	127.3 (35.4)	116.1 (39.2)	105.3 (29.0)

Table 3: Means and Standard Deviations for scores on all 16 neuropsychological tests for each of the 8 groups. BSRT Total = Buschke Selective Reminding Test, Total Recall; BSRT LTR = Buschke Selective Reminding Test, Long Term Recall; BSRT CLTR = Buschke Selective Reminding Test, Consistent Long Term Recall; BSRT Delay = Buschke Selective Reminding Test, Delayed Recall; TMT B = Trail Making Test part B; Stroop CW = Stroop Color Word Interference; WAISIV DS = Wechsler Adult Intelligence Scale IV, Digit Span; TMT A = Trail Making Test part A; WAISIV CD = Wechsler Adult Intelligence Scale IV, Coding; WAISIV SS = Wechsler Adult Intelligence Scale IV, Symbol Search; BNT = Boston Naming Test; FTT DH = Finger Tapping Test, Dominant Hand; FTT NDH = Finger Tapping Test, Non-Dominant Hand; GPT DH = Grooved Pegboard Test, Dominant Hand; GPT NDH = Grooved Pegboard Test, Non-Dominant Hand.

Table 4

	Main Effects			Two-Way Interactions			Three-Way Interaction
	APOE	Sleep Quality	Age	APOE x Sleep	APOE x Age	Sleep x Age	APOE x Sleep x Age
	(p-value)	(p-value)	(p-value)	(p-value)	(p-value)	(p-value)	(p-value)
Memory							
<i>BSRT Total</i>	0.714	0.665	<0.001*	0.691	0.915	0.223	0.111
<i>BSRT LTR</i>	0.855	0.687	<0.001*	0.604	0.901	0.372	0.167
<i>BSRT CLTR</i>	0.899	0.721	<0.001*	0.605	0.845	0.179	0.033*
<i>BSRT Delay</i>	0.971	0.431	0.064†	0.444	0.461	0.177	0.483
Executive Function							
<i>TMT B</i>	0.387	0.578	0.001*	0.466	0.986	0.899	0.021*
<i>Stroop CW</i>	0.219	0.227	<0.001*	0.522	0.889	0.972	0.120
<i>WAISIV DS</i>	0.357	0.971	0.045*	0.333	0.808	0.958	0.436
Processing Speed							
<i>TMT A</i>	0.216	0.716	0.004*	0.875	0.341	0.690	0.004*
<i>WAISIV CD</i>	0.113	0.518	<0.001*	0.391	0.277	0.693	0.148
<i>WAISIV SS</i>	0.165	0.286	<0.001*	0.970	0.832	0.642	0.420
Language							
<i>Category Fluency</i>	0.266	0.164	<0.001*	0.877	0.301	0.835	0.282
<i>BNT</i>	0.702	0.537	0.047*	0.153	0.286	0.705	0.274
Motor Speed							
<i>FTT DH</i>	0.601	0.447	0.001*	0.794	0.552	0.068†	0.322
<i>FTT NDH</i>	0.104	0.211	0.003*	0.993	0.609	0.259	0.432
<i>GPT DH</i>	0.397	0.914	<0.001*	0.732	0.089†	0.054†	0.990
<i>GPT NDH</i>	0.409	0.508	<0.001*	0.405	0.055†	0.716	0.219

Table 4: Main effects for APOE Carrier Status, Sleep Quality, and Age for all 16 of the neuropsychological tests used to assess cognitive function. Two-way interactions between APOE ε4 carrier status and sleep quality, APOE carrier status and age, and sleep quality and age. Three-way interaction between APOE carrier status, sleep quality, and age. (*) Significant effects after controlling for gender, education, hypertension status, years smoked, and Geriatric Depression Scale score (p<0.05). (†) Trend toward significance (p<0.09). BSRT Total = Buschke Selective Reminding Test, Total Recall; BSRT LTR = Buschke Selective Reminding Test, Long Term Recall; BSRT CLTR = Buschke Selective Reminding Test, Consistent Long Term Recall; BSRT Delay = Buschke Selective Reminding Test, Delayed Recall; TMT B = Trail Making Test part B; Stroop CW = Stroop Color Word Interference; WAISIV DS = Wechsler Adult Intelligence Scale IV, Digit Span; TMT A = Trail Making Test part A; WAISIV CD = Wechsler Adult Intelligence Scale IV, Coding; WAISIV SS = Wechsler Adult Intelligence Scale IV, Symbol Search; BNT = Boston Naming Test; FTT DH = Finger Tapping Test, Dominant Hand; FTT NDH = Finger Tapping Test, Non-Dominant Hand; GPT DH = Grooved Pegboard Test, Dominant Hand; GPT NDH = Grooved Pegboard Test, Non-Dominant Hand.

Figure 1

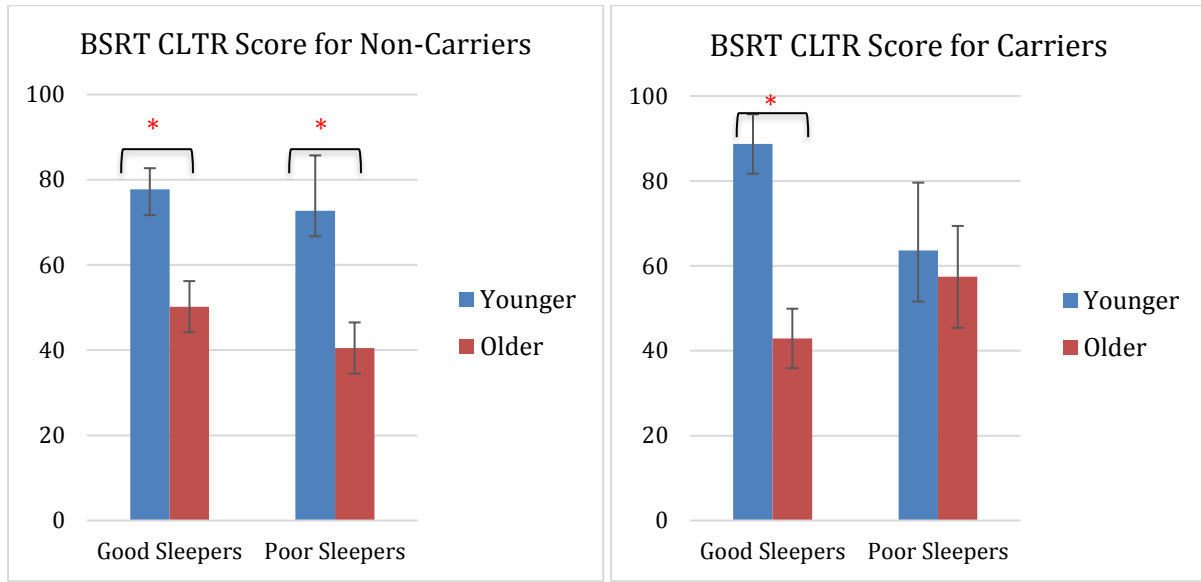


Figure 1. Three-way interactive effects of APOE $\epsilon 4$ carrier status, sleep quality, and age on performance on the BSRT CLTR ($p=0.033$) after controlling for gender, education, self-reported hypertension status, years smoked, and Geriatric Depression Scale score. Significant age effects were found among both good sleepers and poor sleepers within the non-carrier group, as well as among good sleepers in the carrier group (*) $p<0.05$.

Figure 2

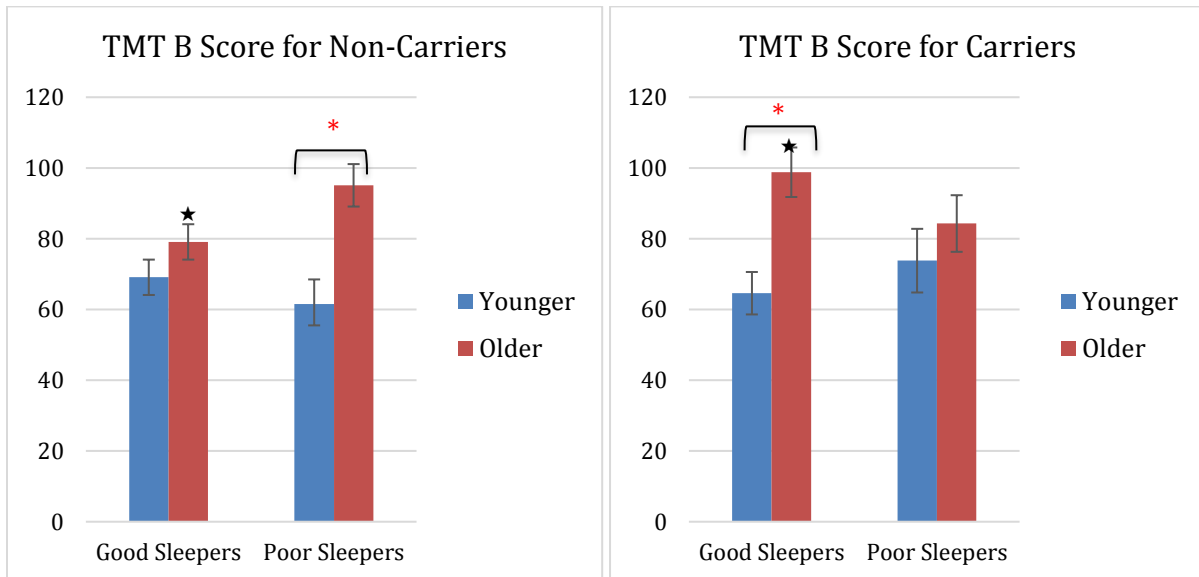


Figure 2. Three-way interactive effects of APOE $\epsilon 4$ carrier status, sleep quality, and age on TMT B performance ($p=0.004$) after controlling for gender, education, self-reported hypertension status, years smoked, and Geriatric Depression Scale score. Higher scores indicate worse performance. Significant age effects were found among non-carriers with poor sleep quality and among carriers with good sleep quality (*) $p<0.05$, with the older group taking longer to complete the task in both groups. Among older participants with good sleep quality, significant effects were found for carrier status (★) $p<0.05$, with carriers performing worse than non-carriers.

Figure 3

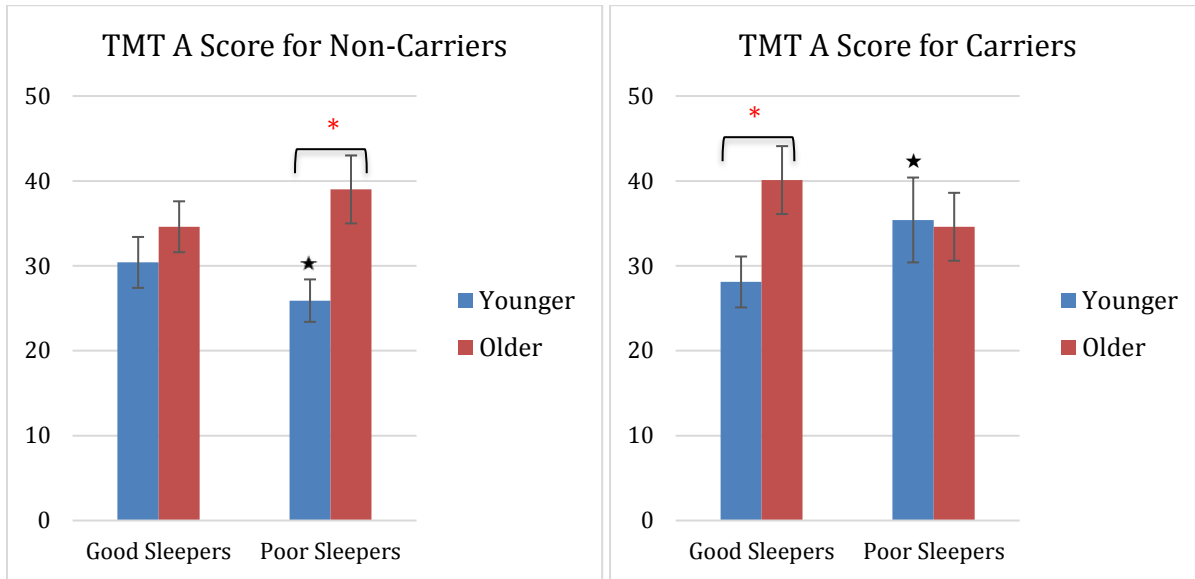


Figure 3. Three-way interactive effects of APOE ϵ 4 carrier status, sleep quality, and age on TMT A performance ($p=0.004$) after controlling for gender, education, self-reported hypertension status, years smoked, and Geriatric Depression Scale score. Higher scores indicate worse performance. Significant age effects were found among non-carriers with poor sleep quality and carriers with good sleep quality (*) $p<0.05$, with the older group taking longer to complete the task in both groups. Significant effects were found across carrier status within the younger poor sleeper group (★) $p<0.05$, with carriers performing worse than non-carriers.

DISCUSSION

The older age group performed worse, on average, on tests of cognitive functioning across all domains measured. The main effects found for age are consistent with what would be expected based on existing research. These findings strongly support the hypothesis that chronological age has a significant negative correlation to many different measures of cognitive ability. As predicted, memory was very strongly impacted by age differences.

Results of this study found no significant main effects for APOE carrier status, necessitating the rejection of the hypothesis that APOE ϵ 4 non-carriers would significantly outperform carriers on measures of memory and executive function. There were also no significant main effects found for sleep quality, which suggests that, in this sample, poor sleep

quality was not associated with worse performance in cognitive domains such as executive function, motor speed, and memory.

The trends towards significant two-way interactions between both APOE carrier status and age as well as sleep quality and age on measures of motor speed suggest that this domain may be sensitive to age when there is another risk factor present, but more research is needed perhaps with larger samples to examine this question further.

This study found a three-way interaction between age, APOE genotype, and sleep quality on a measure of memory (BSRT CLTR), a measure of executive function (TMT B), and a measure of processing speed (TMT A). Follow-up pairwise tests indicated that age had a significant effect in certain groups across all three tests and that carrier status also had a significant effect in specific samples on measures of executive function and processing speed. No significant simple effects were observed for sleep quality.

Specifically, on the BSRT CLTR, significant age effects were found among both good sleepers and poor sleepers within the non-carrier group as well as among good sleepers in the carrier group (Figure 1). For each of these three groups, older participants performed significantly worse than their younger counterparts.

For TMT B, significant effects were found for carrier status among older participants with good sleep quality, with carriers performing worse than non-carriers. Significant age effects were found among non-carriers with poor sleep quality and among carriers with good sleep quality, with the older group taking longer to complete the task in both groups (Figure 2).

Similarly, for TMT A, significant age effects were also found among non-carriers with poor sleep quality and carriers with good sleep quality, with the older group again taking longer to complete the task in both groups. However, for this test, significant carrier status effects were

found for younger participants with poor sleep quality, with carriers performing worse than non-carriers (Figure 3).

Although these results are not entirely consistent across the three measures of cognitive function, they do point to some interesting findings. All three tests showed a significant age effect for non-carriers who had poor sleep quality. On all three tests, the older group had worse scores than the younger group, potentially indicating that younger non-carriers are less susceptible to the deleterious effects of poor sleep quality. These results may be due to the sleep structure changes that occur in older age, such as decreased amplitude and density of slow waves and reduction of neurons that promote wakefulness. These findings support the hypothesis that age would moderate the risk of poor sleep quality.

All three tests also showed a significant age effect for carriers who reported poor sleep quality, with the older group again yielding worse outcomes on all tests. These results may indicate that the harmful effects of combining poor sleep quality and APOE $\epsilon 4$ carrier status may have a significantly greater impact in older age. This result may be explained by the relationship between carrying the $\epsilon 4$ allele and slow wave sleep (Tranah et al., 2018).

We also observed a significant carrier status effect among older good sleepers on TMT B, with carriers performing worse than non-carriers. This result is supported by previous studies (Raichlen & Alexander, 2014), which have indicated that executive function is susceptible to APOE genotype.

The lack of a significant age effect among carriers who are poor sleepers may be due to worse cognitive functioning among the younger participants in this group. Although TMT A is the only test on which there was a significant APOE $\epsilon 4$ carrier status effect for younger poor sleepers, carriers had worse mean scores on all three tests than their non-carrier peers. Since

being an $\epsilon 4$ carrier is linked to an earlier onset age for dementia, it is possible that the added effect of being a carrier and having poor sleep quality is leading this group to experience age-related cognitive decline at a younger age than their peers. Another potential explanation of this lack of an effect focuses on the surprisingly good performance of the older participants within the carrier poor sleeper group. The older group performed in a comparable way to the younger group on all three tests, even outperforming them slightly on TMT A. Phillip et al. (2004) and Stenuit & Kerkhofs (2005), have suggested that older individuals may actually be less susceptible to poor sleep than younger people, likely because they have adapted and developed compensatory mechanisms to compensate for the declines they are facing. It is possible that these older carriers with poor sleep quality began experiencing cognitive declines in their 50s or 60s (as is suggested by the results for the younger carriers with poor sleep), and that they developed ways to compensate for these deficits. Although none of these results were statistically significant, older carriers with poor sleep also had better average scores on all three tests than older carriers with good sleep, which could also potentially be explained by those with poor sleep being forced to develop compensatory skills earlier in life to overcome the deficits caused by their lack of quality sleep. Additional research is needed to address this further.

The finding that age had a significant effect among non-carriers with good sleep quality on the BSRT CLTR did not match up with the results of the other two tests, but this may be because memory is more sensitive to the effects of age than other measures of cognitive function such as executive function and processing speed.

The results found by this study may have been impacted by the health of the original sample. Since stringent exclusionary criteria were applied, potential subjects who were noticeably cognitively impaired or were afflicted by a condition such as sleep apnea or

depression were not included in the sample, reducing the diversity of the group. A more broadly representative sample of this age group may have yielded significant results that were not measurable in this particular cohort.

Another limitation of the current study was that it relied entirely on subjective measures of sleep quality. The PSQI asks participants to self-report about their sleep habits and sleep quality. The subjective nature of this questionnaire leaves room for error, as participants might not be able to accurately remember their recent sleep habits or have become accustomed to low sleep quality. Van Dongen et al. (2003) found that participants who were placed on a chronic sleep restriction schedule reported high levels of daytime sleepiness for the first few days, followed by a return to almost normal levels of self-reported sleepiness, even though their objective impairment continued to grow. This indicates that our brains may “renormalize” after experiencing prolonged sleep deprivation. Future studies might make use of a more objective measure of sleep quality—such as actigraphy—a more accurate measure of sleep.

A larger sample size would also help ensure the reliability of the study results. Two of the groups (older APOE ϵ 4 carriers with poor sleep and younger APOE ϵ 4 carriers with poor sleep) were limited ($n=9$ and $n=8$, respectively), which may have had an impact on the results obtained. Small sample sizes can often decrease the likelihood of detecting significant effects as well as increase the likelihood of having a “false positive” result.

In a follow-up study with a larger sample size, it would be interesting to evaluate APOE genotypes and explore whether the specific genotype has a significant impact compared to solely looking at carrier status. Specifically, it would be interesting to see whether APOE ϵ 4 homozygotes are markedly different from APOE ϵ 4 heterozygotes and whether the “protective” ϵ 2 allele has an interactive effect with sleep quality and age.

Despite the limitations of this study, we did find three significant three-way interactions between APOE carrier status, sleep quality, and age representing effects within the domains of processing speed, executive function, and memory. Follow-up testing showed that there were overarching indications that, among non-carriers, poor sleep seems to make participants more susceptible to the effects of older age on measures of processing speed, executive function, and memory and that APOE $\epsilon 4$ carrier status appears to exacerbate the negative effects of poor sleep among the younger group, as well as the effect of age for participants with good sleep quality.

The results of this study indicate that there may be an important relationship between APOE $\epsilon 4$ carrier status, self-reported sleep quality, and age. Understanding this relationship better could help prove useful for finding successful interventions to reduce the risk of developing AD among the aging population. Further research is needed to discern the exact nature of the interaction between APOE genotype and sleep quality and how this relationship changes across the human lifespan.

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