TITLE.
APOE4 homozygotes have less sleep fragmentation in late adulthood.

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FUNDING.
This work was supported by the National Institute of Health (P30AG021342) and the Alzheimers Association (AARFD-24-1306796).

DISCOLSURES.
Outside of the current work, Orfeu M. Buxton discloses that he received two subcontract grants to Penn State from Mobile Sleep Technologies (NSF/STTR #1622766, NIH/NIA SBIR R43-AG056250, R44-AG056250), received honoraria/travel support for lectures from New York University, Tufts School of Dental Medicine, University of Utah, University of Arizona, and University of Miami; consulting fees from Georgia State University and Harvard Chan School of Public Health; and receives an honorarium for his role as the Editor in Chief of Sleep Health sleephealthjournal.org.

Gawon Cho, Anne Chen, Eunyoung Choi, Daniel Kay, and Brienne Miner do not have financial support to declare and report absence of conflict of interest.

ABSTRACT (250 words)

Study objectives

The presence of APOE4, a genetic risk factor for Alzheimer's Disease (AD), is associated with reduced functional connectivity of brain regions that regulate sleep, which may predispose persons to AD via altered sleep architecture. However, little is known about differences in sleep architecture by *APOE* genotype, and whether they vary by age and sex.

Methods

This cross-sectional study examined the association between *APOE* genotype and sleep architecture, using in-home polysomnography (Sleep Heart Health Study, N=3,107). *APOE* genotype included: *APOE4* heterozygotes, *APOE4* homozygotes, *APOE2* carriers, and *APOE3* homozygotes (reference). Sleep architecture was quantified using the percentage of time spent in rapid eye movement sleep (%REM), N1 (N1%), N2 (%N2), N3 (%N3), and arousal index. Linear regression was employed, adjusting for age, sex, marital status, race, education, and parent cohort. Interactions with age and sex-stratified analyses examined variations by age and sex, respectively.

Results

The median age was 67 years, 27.4% carried at least one *APOE4 allele*, and 52.9% were females. Without age by *APOE* genotype interaction, %REM, %N1, %N2, %N3, and arousal index were comparable across *APOE* genotypes in the full sample, males, and females. When an age by *APOE* genotype interaction was introduced, *APOE4* homozygotes showed fewer arousals with each year of age (β=-0.33 arousals, p=0.04), leading to significantly less arousals at age ≥70 (marginal difference=-2.98, p=0.04).

Conclusions

Compared with APOE3 homozygotes, APOE4 homozygotes showed comparable proportions of REM, N1, N2, and N3, but exhibited fewer arousals in old age. *APOE4* homozygotes may have an elevated arousal threshold.

Key words

Sleep architecture, *APOE* genotype, Alzheimer's disease, sleep fragmentation, arousals, wake after sleep onset

1. INTRODUCTION

The *apolipoprotein E ε4* (*APOE4*) is the most established genetic risk factor for Alzheimer's disease (AD), a progressive neurodegenerative disorder affecting more than six million older adults in the United States. [1] *APOE*4 carriers, including heterozygotes and homozygotes, exhibit reduced functional connectivity of key neuromodulatory regions that regulate sleep, including the basal forebrain[2] and the locus coeruleus. [3] These regions are central to the regulation of sleep stage transitions that define sleep architecture, including rapid eye movement (REM) and non-REM sleep stages (N1, N2, and N3 or slow-wave sleep [SWS]). [4-8] Disrupted connectivity involving these regions in *APOE4* carriers may render them more susceptible to alterations in sleep architecture, a known risk factor for AD and related dementias. [9-12] Thus, impaired sleep architecture may be a mechanistic pathway linking *APOE4* genotype to elevated AD risk.

Empirical evidence examining the relationship between *APOE* genotype and sleep architecture in middle-aged and older adults is limited. To date, two studies have investigated the relationship between *APOE*4 genotype and sleep architecture, reporting inconsistent findings. [13,14] Importantly, both studies were conducted in relatively smaller samples with limited representation of *APOE4* carriers, particularly homozygotes, limiting statistical power to detect robust genotype-specific effects. Furthermore, both studies focused exclusively on older adults, i.e., a population in which sleep disturbances are prevalent regardless of genetic risk. [15-17] Whether genotype-related differences in sleep architecture may be more detectable in middle age has not been investigated. Finally, only one of the two studies included women, [14] an important subgroup to examine given their higher rates of both AD and sleep disturbances. [18-21] Notably, *APOE4* appears to confer greater AD risk in women, [22] underscoring the need to characterize sleep architecture specifically in female *APOE4* carriers.

To address these gaps, the present study investigated the association between *APOE* genotype and sleep architecture in a large, community-based sample of middle-aged men and women, with robust representation of *APOE4* heterozygotes and homozygotes. Because the presence of an *APOE4* allele has been associated with reduced functional connectivity in brain regions involved in regulating sleep stage transitions, [4-8] we hypothesized that *APOE4* carriers would exhibit altered sleep architecture - characterized by reduced REM sleep and SWS, as well as increased arousals - relative to non-carriers. We further hypothesized that genotype-associated differences would be more pronounced in middle age than late adulthood, since sleep disturbances in late adulthood are more common regardless of genetic risk. Lastly, given prior evidence showing that *APOE4* confers greater risk for AD in women, we explored whether carrying an *APOE4* is differently associated with sleep architecture between females and males. These investigations are required as the first step in evaluating whether alterations in sleep architecture may represent a modifiable risk factor for AD among *APOE4* carriers.

2. METHODS

2.1. Study Sample

The Sleep Heart Health Study (SHHS) is a multi-center, community-based cohort study designed to investigate relationships between sleep disorders and health outcomes in U.S. adults. Details of the study design and data collection protocols have been described previously. [23] Briefly, between 1995 and 1998, the SHHS enrolled 6,441 adults aged 40 years and older from several established parent cohorts, including the Atherosclerosis Risk in the Community Study (ARIC), [24] the Cardiovascular Health Study (CHS), [25] the Framingham Heart Study (FHS), [26] among a few others. [27] [28] [29] The enrolled participants subsequently completed a single night of unattended, in-home overnight polysomnography. [23] Blood samples were collected by the parent cohorts, facilitating *APOE* genotyping.

For the current study, we included participants who completed overnight polysomnography and had available *APOE* genotype data. Because *APOE* genotype was publicly available in only a subset of the parent cohorts (i.e., ARIC, CHS, and FHS), our analytic sample was restricted to participants recruited from these three cohorts. From 3,817 individuals from the ARIC, CHS, or FHS who had complete polysomnography data, 324 were excluded due to missing information on *APOE* genotype, and 232 were excluded due to missing data on other covariates. We further excluded 154 individuals under the age of 50 and those who were 85 or older to examine robust age-related trends. The final analytic sample included 3,107 participants (see Supplementary Figure S1). All study procedures were approved by the Yale University Institutional Review Board.

2.2. Outcomes

The primary outcomes were sleep architecture variables derived from overnight in-home polysomnography, including the proportion of rapid eye movement sleep (%REM), the proportion of non-REM sleep stages (%N1, %N2, and %N3 or slow-wave sleep [%SWS]), and arousal index (arousals per hour). Detailed procedures for data acquisition, processing, and sleep stage scoring have been described previously.[23] Briefly, the Compumedics PS system (Abbotsford, Victoria, Australia) was used to perform full-montage polysomnography following standardized protocols, including electroencephalography (EEG), electrooculography, chin electromyography, thoracic and abdominal plethysmography, airflow, pulse oximetry, electrocardiography, and body position monitoring.[23] Sleep stages and arousals were manually scored in 30-second epochs according to the American Academy of Sleep Medicine criteria.[23,30,31] Percent time spent in each sleep stage (%REM, %N1, %N2, and %SWS) was calculated by dividing the duration of each stage by the total sleep time, allowing for normalization across individuals with varying sleep durations. The arousal index was computed as the number of arousal events per hour of total sleep time.

Post hoc analyses examined two additional sleep characteristics derived from polysomnography. These included total sleep time (in minutes) and wake after sleep onset (WASO; total time spent awake between sleep onset and offset).

2.3. Exposure

APOE carrier status was categorized into the following four groups based on genotyping performed using DNA extracted from whole blood: *APOE4* heterozygotes (ε2/ε4 or ε3/ε4), *APOE4* homozygotes (ε4/ε4), *APOE2* carriers (ε2/ε2 or ε2/ε3), and *APOE3* homozygotes (ε3/ε3). *APOE4* heterozygotes and homozygotes were analyzed as distinct groups to assess potential dose-dependent effects of *APOE4*. *APOE2* carriers were categorized separately, given that some studies found *APOE2* to be associated with increased cardiovascular risk, [32] which may impact sleep architecture. *APOE3* homozygotes served as the reference group as they are the population majority and have the lowest risk of AD. [20] Detailed protocols for blood collection, DNA isolation, and *APOE* genotyping have been described previously. [33-35]

2.4. Statistical Analysis

Differences in sample characteristics by *APOE* genotype were assessed using ANOVA for continuous variables and chi-square for categorical variables. To examine unadjusted average sleep architecture by *APOE* genotype throughout the age span, we visualized non-linear age trajectories using kernel-weighted local polynomial smoothing with a bandwidth of 5. This non-parametric approach allowed for flexible modeling of age trends in sleep outcomes without imposing specific functional forms. We then assessed the association between *APOE* genotype and each sleep variable using parametric linear regression models, adjusting for age, sex, race, marital status, educational attainment, and parent cohort. Analyses were conducted in the full sample and stratified by sex to evaluate potential differences between males

and females. Moreover, to test whether age moderated the relationship between *APOE* genotype and sleep architecture, we introduced interactions between *APOE* genotype and age, using both linear and quadratic terms. For outcomes with significant interactions, we estimated marginal differences by *APOE* genotype across the age span using recycled predictions. These predictions were generated by varying *APOE* genotype and age while holding all other covariates at their observed values. Age was zero-centered around the sample median to improve applicability of regression estimates to the sample's age range. Post-hoc analyses examined the association of the total sleep time and WASO with *APOE* genotype. Statistical significance was defined at the level of $p < 0.05$. All analyses were conducted using Stata MP, version 17 (StataCorp, College Station, TX).

3. RESULTS

Table 1 shows the characteristics of the analytic sample. The median age was 67 (interquartile range [IQR]=59-74), 52.9% were female, and 95.7% were White. Eighty four percent were married and 34.9% completed $\geq$16 years of education. Median proportions of REM sleep (%REM) and SWS (%SWS) were 20.2% and 17.6%, respectively. Individuals had a median of 17.2 arousals per hour. A total of 786 persons (25.3 %) carried one *APOE4* allele and 66 (2.1%) carried two *APOE4* alleles. All sample characteristics were comparable across *APOE* genotype, except for race, where the proportion of *APOE2* carriers were lower among White individuals.

Figure 1 displays unadjusted average sleep architecture by *APOE* genotype throughout the age span, produced using kernel-weighted local polynomial smoothing. Across all genotypes, %REM sleep declined monotonically with age. In all genotypes, %N1 increased with age until approximately 70, after which it plateaued, although *APOE4* homozygotes exhibited a modest decline thereafter. %N2 increased steadily with age for all groups, with *APOE4* homozygotes demonstrating the steepest increase. In

contrast, %SWS declined with age across all genotypes, with the most pronounced reduction observed in *APOE4* homozygotes. Lastly, arousal index increased with age in all genotypes, except among *APOE4* homozygotes, who exhibited a decreasing trend until age 70, after which it plateaued. Unadjusted age trajectories of total sleep time and WASO are presented in Supplementary Figure 2. Total sleep time exhibited a monotonic decreasing trend in *APOE3* homozygotes and *APOE4* heterozygotes, while *APOE2* carriers and *APOE4* homozygotes showed relatively stable sleep duration across the age span. All genotypes showed monotonic increases in WASO with age, except for *APOE4* homozygotes, among whom WASO began to decline in the late 60s.

Table 2 presents the association between sleep architecture and *APOE* genotype, estimated using models adjusted for all covariates. In models without interaction terms, %REM, %N1, %N2, %SWS and arousal index did not differ significantly by genotype. In models that additionally included an interaction between age and *APOE* genotype, the association between *APOE* genotype and arousal index was found to vary with age, where *APOE4* homozygotes showed 0.33 fewer arousals per hour per year of age after the sample median age of 67 (i.e., as age was median-centered) than *APOE3* homozygotes (p=0.04). This led to *APOE4* homozygotes having significantly fewer arousals than *APOE3* homozygotes at age 70 and beyond, but not at age 65 or before (Figure 2A, marginal difference at age 70=2.98, p=0.04). For instance, at age 75, *APOE4* homozygotes exhibited 4.64 arousals per hour (p=0.02). The interaction between *APOE* genotype and a quadratic age term was not significant in all models (results not shown). In sex-stratified models adjusted for all covariates, all components of sleep architecture remained comparable across *APOE* genotypes in both men and women (Supplementary Table 1).

Additional analyses examining total sleep time and WASO found that the association between *APOE* genotype and WASO varied by age, where *APOE4* homozygotes experienced 1.8 fewer minutes of

WASO per year of age after the sample median age relative to *APOE3* homozygotes, but 1.8 more minutes of WASO before the sample median age (p = 0.01; Table 3). As shown in Figure 2B, this led to WASO remaining relatively stable among *APOE4* homozygotes across the age span, whereas it increased monotonically among *APOE3* homozygotes. Compared to *APOE3* homozygotes, *APOE4* homozygotes 26.35 more minutes of WASO at age 50 (p = 0.03), but 17.37 less minutes of WASO at 75 (p = 0.03). Sex-stratified analyses found that total sleep time and WASO remained comparable across *APOE* genotypes in both men and women (see Supplementary Table 2).

4. DISCUSSION

In a large sample of community-dwelling middle-aged and older adults, we found that *APOE4* homozygotes and heterozygotes spent comparable proportions of time in REM, N1, N2, and SWS, regardless of age and sex. However, in late adulthood, arousal index and WASO - both of which are markers of sleep fragmentation - were significantly lower in *APOE4* homozygotes compared with *APOE3* homozygotes. *APOE4* heterozygotes exhibited comparable arousal index and WASO across age as *APOE3* homozygotes. To summarize, our study found that *APOE4* carriers exhibited comparable overnight sleep architecture as *APOE3* homozygotes, but *APOE4* homozygotes were less likely to experience sleep fragmentation in late adulthood.

Motivation behind the current study was to investigate whether sleep architecture may serve as an underlying pathway linking the *APOE4* allele to elevated AD risk. We hypothesized that *APOE4* carriers may experience more deficient sleep due to early neurodegeneration and dysfunctional communication of sleep-regulating brain regions, including the basal forebrain and locus coeruleus. [5-8,36] Contrary to this hypothesis, *APOE4* carriers - both male and female - were found to exhibit largely comparable sleep architecture as non-carriers during middle and late adulthood. *APOE4* homozygotes were also found to

show less sleep fragmentation in late adulthood. These findings suggest that impairments in sleep architecture may not be the primary pathway through which *APOE4* genotype contributes to AD progression. Nonetheless, it should be noted that our analyses focused on macrostructural aspects of sleep architecture. Future work should evaluate whether *APOE4* carriers exhibit microstructural qualities of sleep that have been associated with neurocognitive impairment, such as K-complex density. [37]

Interestingly, this study robustly found lower arousal index and WASO among *APOE4* homozygotes relative to *APOE3* homozygotes in late adulthood. These findings suggest that *APOE4* homozygotes exhibit less sleep fragmentation, which is contrary to our initial hypothesis stating that *APOE4* allele would be associated with impaired sleep architecture, including more sleep fragmentation. On one hand, these findings could suggest that *APOE4* homozygotes have better sleep quality later in life. Nonetheless, interpreting the observed associations of lower arousal index and WASO with *APOE4* homozygosity during late adulthood requires caution. Such decreases in sleep fragmentation were not accompanied by greater times spent in REM or SWS, both of which have been associated with neurocognitive benefits. [9,37,38] On the contrary, the visualization of unadjusted age trends found *APOE4* homozygotes to exhibit the steepest decline in SWS. These findings raise the possibility that lower levels of sleep fragmentation in *APOE4* carriers may not reflect truly restorative sleep. [2,3] Rather, less sleep fragmentation may reflect elevated arousal thresholds due to neurodegeneration, potentially, of regions that regulate sleep and wake including the locus coeruleus and basal forebrain. [5-8,36,39]

In addition, *APOE4* homozygotes exhibited stable levels of arousal index and WASO across the age span observed in this study, which led them to exhibit a trend towards higher arousal index before the age of 60, along with significantly higher WASO at age 50. While further evidence is needed, these findings raise the possibility that *APOE4* homozygotes may begin experiencing high levels of sleep fragmentation

earlier on during in adulthood than *APOE3* homozygotes, highlighting the need for research on age trajectories of sleep by *APOE* genotype across the entire lifespan. If it is determined that APOE4 homozygotes experience more sleep fragmentation during early stages of adulthood, sleep fragmentation may represent a plausible pathway linking the *APOE4* genotype to increased *AD* burden.

To date, two studies have examined the association between *APOE* genotype and sleep architecture, reporting heterogeneous findings. Tranah et al. examined community-dwelling older men (mean age=77 years; N=2,302, including 515 *APOE4* heterozygotes and 40 homozygotes) and found that *APOE4* homozygotes had longer SWS and shorter WASO compared to non-carriers, while REM and N1 durations remained comparable across *APOE* genotype. [13] Our findings are partially consistent with those of Tranah et al. [13] as we found *APOE4* homozygotes to have fewer arousals and shorter WASO in their 70s and beyond than non-carriers, along with comparable levels of REM and N1. However, we did not find *APOE4* carriers to have longer SWS, potentially due to our operational definition of SWS as its proportion out of total sleep time, which can be different from its absolute duration used by Tranah et al. Moreover, Andre et al. examined a smaller, mixed-sex sample (mean age=69 years; N = 198, including 41 heterozygotes and 5 homozygotes) and reported that *APOE4* carriers (without distinguishing between heterozygotes and homozygotes) had shorter REM sleep, both in absolute duration and as a proportion of total sleep time. [14] They did not find differences in SWS and WASO. [14] Similar to Andre et al., [14] we found individuals to spend comparable proportions of their sleep in SWS across *APOE* genotype. However, our findings on WASO and REM sleep largely diverge from their study, as *APOE4* homozygotes were found to have shorter WASO in late adulthood, along with comparable proportions of REM sleep as non-carriers. These differences may reflect the larger number of *APOE4* heterozygotes and homozygotes in our study, which allowed us to distinguish between the two genotypes. Collectively, the majority of studies to date suggests that *APOE4* homozygotes may experience less sleep fragmentation in late adulthood. Further

validation studies are required to clarify the impact of *APOE* genotype on REM and SWS, particularly by distinguishing between *APOE4* homozygotes from heterozygotes.

The strengths of the current study include the following. First, this study used gold-standard methods to assess a comprehensive set of sleep characteristics previously linked to Alzheimer's disease risk[10,40] in community-dwelling adults, enhancing the applicability of the findings to *APOE4* homozygotes found in the general population. Second, the study included the largest number of *APOE4* heterozygotes and homozygotes among all existing studies on this topic. Third, the inclusion of middle-aged adults allowed for the examination of age-related variations in the association between *APOE* genotype and sleep across both middle and late adulthood. Nonetheless, this study is not without limitations. First, polysomnography does not capture all relevant features of sleep health. For instance, daytime napping behavior, which is a sign of non-restorative sleep and a risk factor of AD, [41] may be relevant. Future work should investigate whether napping behavior differs in *APOE4* carriers. Second, we did not examine microstructural features of sleep architecture, such as sleep spindle activity or delta wave density. Third, sleep quality was assessed based on a single night of polysomnography, which may be influenced by the "first-night effect", a well-documented phenomenon wherein sleep is disturbed during the initial night of monitoring. [42] Thus, our estimates of sleep architecture may not reflect individuals' habitual sleep patterns. Fourth, over 90% of the analytic sample identified as White, decreasing generalizability of our results. To address these limitations, future studies should examine the association between *APOE* genotype and sleep using more comprehensive assessments and in more diverse samples.

Conclusions

In our large population-based sample of middle-aged and older adults, *APOE4* heterozygotes and homozygotes spent comparable proportions of times in REM, N1, N2, and SWS as *APOE3* carriers, who are the population majority. These associations did not vary by sex. *APOE4* homozygotes demonstrated lower levels of sleep fragmentation in late adulthood, suggesting this group may have an increased arousal threshold. Future research is needed to clarify changes in sleep fragmentation among *APOE4* carriers across a broader age span and to determine whether reductions in sleep fragmentation with age may represent an underlying pathway contributing to their elevated risk of AD.

Data source.

This Manuscript was prepared using the following Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BIOLINCC) and the Database of Genotypes and Phenotypes (dbGaP). BIOLINCC provided research materials for SHHS, ARIC, and CHS. dbGaP provided research materials for FHS. This study does not necessarily reflect the opinions or views of the SHHS, ARIC, CHS, FHS, the original study investigators, its funders, BIOLINCC, or dbGaP. The Sleep Heart Health Study (SHHS) was supported by National Heart, Lung, and Blood Institute cooperative agreements U01HL53916 (University of California, Davis), U01HL53931 (New York University), U01HL53934 (University of Minnesota), U01HL53937 and U01HL64360 (Johns Hopkins University), U01HL53938 (University of Arizona), U01HL53940 (University of Washington), U01HL53941 (Boston University), and U01HL63463 (Case Western Reserve University). Atherosclerosis Risk in Communities Study (ARIC), carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (75N92022D00001, 75N92022D00002, 75N92022D00003, 75N92022D00004, 75N92022D00005). Cardiovascular Health Study (CHS) was supported by contract numbers N01-HC-85079, N01-HC-85080, N01-HC-85081, N01-HC-85082, N01-HC-85083, N01-HC-85084, N01-HC-85085, N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, N01-HC-85239 and HHSN268201200036C; grant numbers U01 HL080295 from the National Heart, Lung, and Blood Institute and R01 AG-023629 from the National Institute on Aging, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. This manuscript was not prepared in collaboration with CHS investigators and does not necessarily reflect the opinions or views of CHS, or the NHLBI. Finally, this study analyzed datasets collected by the Framingham Heart Study (FHS; dbGaP accession number: phs000007.v33. p14). The Framingham Heart Study is conducted and supported by the National Heart,Lung, and Blood Institute (NHLBI) in collaboration with Boston University (Contract No. N01-HC-25195, HHSN268201500001I and 75N92019D00031). Funding to support the Omni cohort recruitment, retention and examination was provided by NHLBI Contract N01-HC-25195, HHSN268201500001I and 75N92019D00031, as well as NHLBI grants R01-HL070100, R01-HL076784, R01-HL-49869, and U01-HL-053941. This manuscript was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University, or NHLBI. Funding for SHARe Affymetrix genotyping was provided by NHLBI Contract N02-HL-64278. SHARe Illumina genotyping was provided under an agreement between Illumina and Boston University. Funding for Affymetrix genotyping of the FHS Omni cohorts was provided by Intramural NHLBI funds from Andrew D. Johnson and Christopher J. O'Donnell.

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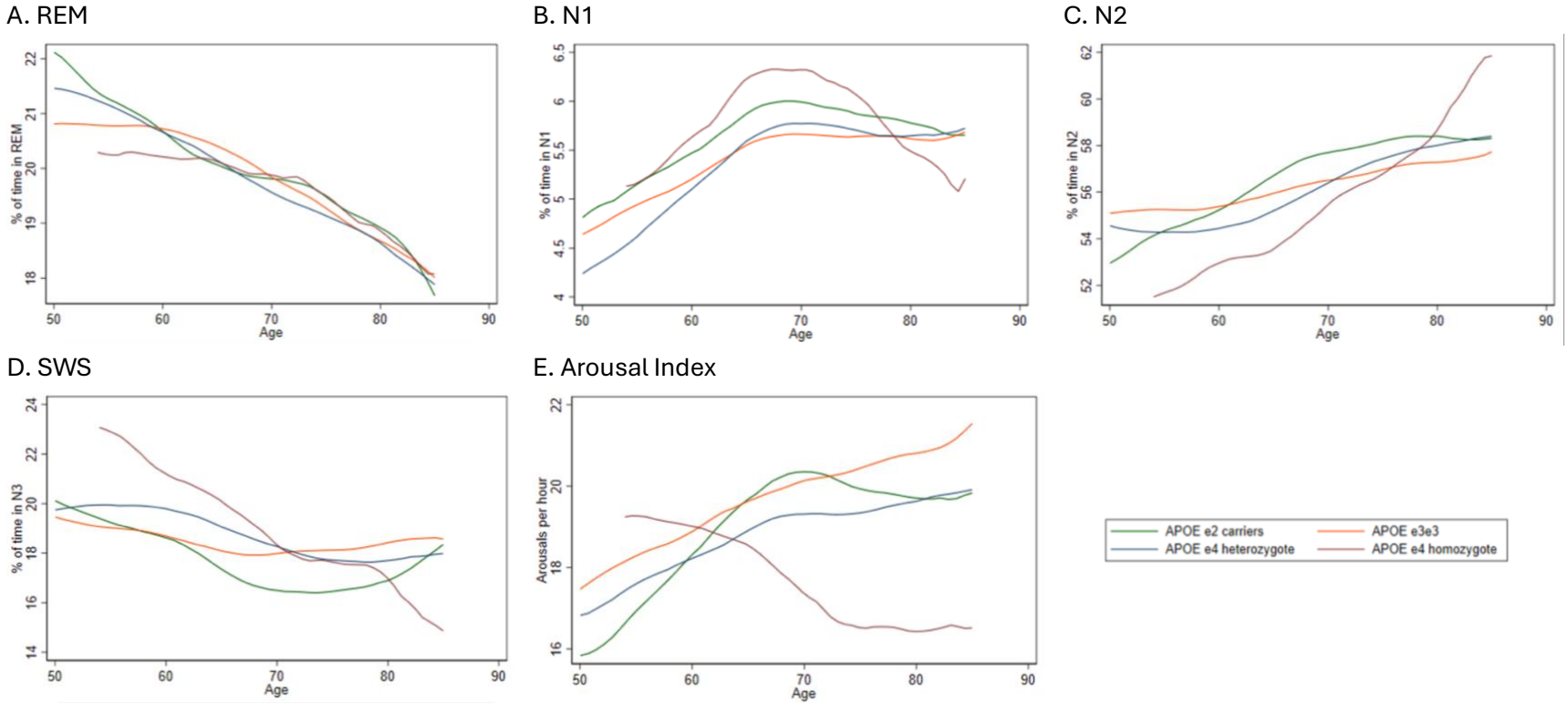
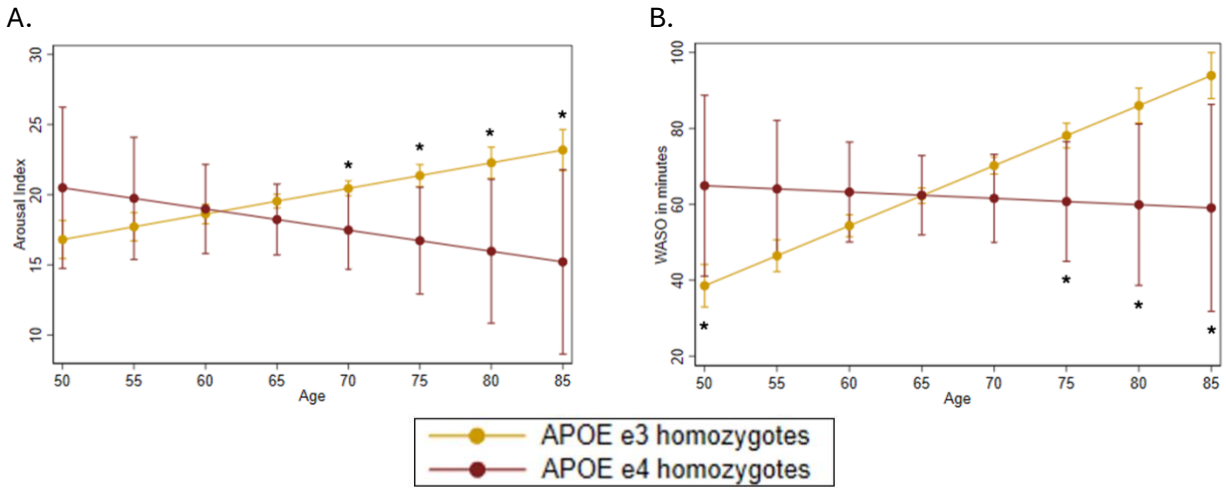
Figure 1. Age trajectories of sleep architecture characteristics by APOE genotype



Acronyms. APOE= apolipoprotein allele; REM=rapid eye movement; WASO=wake after sleep onset

Figure 2. Marginal differences in arousal index, WASO, and total sleep time by *APOE* genotype across the age span



Abbreviation. WASO=wake after sleep onset

Table 1. Sample characteristics

Characteristics	N (%) or median [IQR] [a]					
	Full sample (N=3,107)	*APOE* genotype				
		*APOE*4 heterozygotes[b] (N=786)	*APOE*4 homozygotes (N=66)	*APOE* ε2 carriers[c] (N=411)	*APOE* ε3 homozygotes (N=1844)	*p*[d]
APOE genotype						
***APOE4* heterozygotes**	786 (25.3)					
***APOE4* homozygotes**	66 (2.12)			N/A		
***APOE2* carriers**	411 (13.2)					
***APOE3* homozygotes**	1,844 (59.4)					
Age	67 (59-74)	66 (59-74)	65 (60-73)	67 (59-75)	67 (59-74)	0.80
Sex						0.70
Males	1,465 (47.2)	365 (24.9)	27 (1.84)	193 (13.2)	880 (60.1)	
Females	1,642 (52.9)	421 (25.6)	39 (2.4)	218 (13.3)	974 (58.7)	
Race						0.002
White	2,939 (94.6)	744 (25.3)	62 (2.11)	373 (12.7)	1,760 (59.9)	
Non-White	168 (5.4)	42 (25.0)	4 (2.38)	38 (22.6)	84 (50)	
Marital status						0.33
Married	2,603 (83.8)	783 (25.9)	53 (2.04)	338 (13.0)	1,539 (59.1)	
Not married	504 (16.2)	113 (22.4)	13 (2.6)	73 (14.5)	305 (60.5)	
Educational attainment						0.60
15 years or less	2,023 (65.1)	511 (25.3)	41 (2.03)	257 (12.7)	1,214 (60.0)	
16 years or longer	1,084 (34.9)	275 (25.4)	25 (2.3)	154 (14.2)	630 (58.1)	
Sleep architecture						
%REM	20.2 (16.1-24.0)	20.4 (15.9-24.2)	20.5 (16.0-23.9)	20.1 (16.2-23.7)	20.1 (16.1-23.9)	0.95
%N1	4.6 (2.8-7.1)	4.6 (2.8-6.8)	5.2 (2.8-7.5)	4.6 (2.8-7.5)	4.6 (2.8-7.1)	0.80
%N2	56.5 (48.6-64.5)	56.1 (48.1-64.0)	54.1 (46.7-61.6)	56.7 (49.6-65.6)	56.7 (48.8-64.6)	0.42
%SWS	17.6 (9.0-25.9)	17.8 (9.1-26.3)	19.3 (10.6-28.1)	16.7 (8.2-24.9)	17.6 (8.9-25.8)	0.39
Arousal index	17.2 (12.4-24.2)	16.6 (12.0-23.4)	17.5 (12.6-21.8)	17.3 (12.2-23.8)	17.4 (12.6-24.6)	0.10

Alternative measures of sleep						
WASO	53.5 (32-86.5)	51.5 (30.5-85)	46.3 (33-79.5)	55 (33-85.5)	54 (32.5-87.5)	0.62
Total sleep time (min)	316.9 (274.1-355)	316.8 (272.1-354.9)	302.2 (275.3-344.8)	316.2 (272.6-358.4)	317.5 (275.9-355.0)	0.89

[a] N(%) is reported for categorical variables and median (IQR) are reported for continuous variables. Estimates in each genotype group correspond to individuals with a given genotype.
[b] Includes APOE ε4ε2 and ε4ε3 carriers.
[c] Includes APOE ε2ε2 and ε2ε3 carriers.
[d] Comparison of sample characteristics across APOE genotype used chi-square tests for categorical variables and ANOVA for continuous variables.

Acronyms. APOE= apolipoprotein E allele; IQR=interquartile range; REMS=rapid eye movement; SWS=slow wave sleep; WASO=wake after sleep onset

Table 2. Association between *APOE* genotype and sleep architecture [a]

Model		*APOE* genotype [b]					
		***APOE* ε4 Heterozygote**		***APOE* ε4 Homozygote**		***APOE* ε2 carriers**	
	Main effect	**Estimate**	***p***	**Estimate**	***p***	**Estimate**	***p***
No interaction	**%REM**	-0.09	0.74	0.07	0.93	0.18	0.59
	%N1	0.02	0.91	0.36	0.45	0.19	0.38
	%N2	-0.15	0.75	-1.51	0.28	0.18	0.77
	%SWS	0.22	0.64	1.08	0.44	-0.54	0.37
	Arousal index	-0.74	0.10	-1.67	0.20	-0.89	0.12
Age x *APOE*	**Variations with age**	**Estimate[c]**	***p***	**Estimate[c]**	***p***	**Estimate[c]**	***p***
	%REM	-0.04	0.21	0.002	0.98	-0.03	0.39
	%N1	0.01	0.56	-0.07	0.28	-0.008	0.74
	%N2	0.03	0.65	0.16	0.36	0.13	0.07
	%SWS	0.001	0.98	-0.10	0.57	-0.09	0.21
	Arousal index	-0.03	0.60	-0.33	0.04*	0.01	0.81

[a] Covariates include sex, race, marital status, and educational attainment.

[b] Reference group is *APOE* ε3 homozygotes.

[c] Sign should be reversed for ages <67, since age was median-centered (median age =67).

* Denotes statistical significance at the level of $p<.0.05$.

Acronyms. APOE=apolipoprotein E allele; REM=rapid eye movement; SWS=slow wave sleep

Table 3. Association between *APOE* genotype and alternative measures of sleep (post-hoc analyses) [a]

Model		***APOE4* genotype** [b]					
		***APOE* ε4 Heterozygote**		***APOE* ε4 Homozygote**		**APOE 2 carriers**	
		Estimate	***p***	**Estimate**	***p***	**Estimate**	***p***
No interaction	**Total sleep time**	-0.83	0.74	-7.69	0.30	0.97	0.76
	WASO	-1.19	0.51	-1.70	0.75	-1.31	0.58
Age x *APOE*	**Variations with age**	**Estimate** [c]	***p***	**Estimate** [c]	***p***	**Estimate** [c]	***P***
	Total sleep time	0.54	0.07	0.78	0.40	0.93[d]	0.009*
	WASO	0.11	0.59	-1.75	0.01*	-0.23	0.37

Acronyms. REMS=rapid eye movement; SWS=slow wave sleep; WASO=wake after sleep onset

[a] Covariates include sex, age, race, marital status, and educational attainment. Significant interactions were not observed between quadratic age and *APOE* genotype. Thus, results are not included.

[b] Reference group is *APOE3* homozygotes.

[c] Sign should be reversed for ages <67, since age was median-centered (median age =67).

[d] Differences in age trends for total sleep time between APOE42 carriers and *APOE3* homozygotes are shown in Supplementary Figure 3.

* Denotes statistical significance at the level of $p<.0.05$.