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Examining the association between Apolipoprotein E (*APOE*) and self-reported sleep disturbances in non-demented older adults

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Abstract

We aimed to examine the association between apolipoprotein E (*APOE*) and sleep disturbances. This is a cross-sectional study, from the Washington Heights-Inwood Community Aging Project (WHICAP). A total of 1,944 non-demented older adults took part in the study. Sleep dysfunction was measured using sleep categories derived from the RAND Medical Outcomes Study Sleep Scale. Genetic association between *APOE*-ε4 genotype and sleep disturbances was assessed using unadjusted linear regression models. Secondary analyses were conducted adjusting for age, sex, education, ethnicity and body mass index (BMI). In the unadjusted model, individuals carrying the *APOE*-ε4 allele showed lower levels of snoring (β=−0.02, SE= 0.01, p =0.010) and sleep apnea (β=−0.01, SE= 0.01, p =0.037) when compared to non-ε4 carriers. After covariates' adjustment, ε4

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Angeliki Tsapanou: study design, interpretation of the results, preparation of the manuscript, statistical analysis. Dr. Tsapanou reports no disclosure.

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carriers demonstrated stronger association with lower levels of both snoring (β=−0.02, SE= 0.01, *p*=0.006), and sleep apnea (β=−0.01, SE= 0.01, *p*=0.018). Our results suggest that *APOE*-ε4 is associated with decreased problems in snoring and sleep apnea, in non-demented older adults.

Keywords

Apolipoprotein E; aging; older adults; sleep problems

Introduction

Sleep dysfunction is common among the elderly population. Among the most common sleep complaints in the elderly are insomnia (population frequency ranging from 23 to 34%), and difficulty feeling rested upon waking (7–15%) [(1)]. Experimental studies in both animals and humans have demonstrated that disruptions in sleep patterns exert considerable effects on brain health [(2)].

From a genetic prospective, several studies have suggested a familial aggregation of obstructive sleep apnea/hypopnea (OSA/H) [(3, 4)], snoring, and daytime hypersomnolence [(5)]. Results from a large longitudinal twin study showed that insomnia is moderately heritable (14%–38%) [(6)], suggesting that there might be a strong genetic contribution to sleep disturbances.

Apolipoprotein E gene (*APOE*) is known as a major risk factor for Late Onset AD [(7, 8)]. However, studies assessing whether *APOE* gene may contribute to the risk of disturbances in sleep have been scarce, and results are contradictory. One study suggests that apnea/hypopnea is linked to chromosome 19, a region that contains the *APOE* gene [(9)].

Some of the existing studies suggest that individuals carrying the *APOE*-ε4 locus have an increased risk of developing OSA/H [(10)]. Moreover, OSA patients that carry the ε4 *APOE* locus have demonstrated an increased risk of impaired spatial working memory [(11)]. *APOE*-ε4 has also been associated with sleep disordered breathing (SDB) [(12–14)].

On the other hand, studies with OSA patients showed that the frequency of the *APOE*-ε4 allele is the same as in a random population [(15–17)]. According to a study, which compared individuals with different degrees of SDB, there was no association between SDB and *APOE*-ε4 [(18)]. More existing studies found no association between *APOE*-ε4 and OSAS [(16, 19)].

A different study investigating the association among napping, *APOE*-ε4, and dementia, showed that napping for up to 60 minutes had an apparently protective effect against developing AD, especially for the *APOE*-ε4 carriers [(20)].

Among the reasons -that might explain the different results- may be the small sample size of the study cohorts [(11–14, 16, 21–23)]. Moreover, the largest studies to date, (n=1775)[(10)], (n=1211) [(15)], examining the association between *APOE*-ε4 and OSA, were largely focused on White participants, and therefore, limiting the ability to generalize the results to other ethnic groups [(10, 15)]. Some other studies have restricted the analyses to male participants,

which substantially reduces the statistical power to detect possible genetic associations [14, 18]. Lastly, to the best of our knowledge, none of the existing studies using older adults has carefully excluded subjects with mild cognitive impairment (MCI) or dementia.

The aim of the present study was to assess whether *APOE*-ε4 is associated with sleep apnea in a large, and ethnically diverse cohort of non-demented elderly.

We also aimed to examine whether other types of sleep problems would be differentially associated with *APOE*-ε4 in the same sample of participants.

Methods

Participants were drawn from the Washington Heights-Inwood Community Aging Project (WHICAP) at Columbia University Medical Center [24, 25]. WHICAP is a community based research study designed to identify risk factors and biomarkers for aging and Alzheimer's disease in a multi-ethnic cohort that includes Whites, African-Americans, Caribbean-Hispanics, and Other [26]. Evaluations were conducted in either English or Spanish, based on the preference of the participant. Detailed description of the cohort can be found in previous publications [24, 26].

The initial sample consisted of 2,358 participants. As both *APOE*-ε4 and sleep disturbances are prevalent in demented patients, we restricted our analyses to non-demented participants. Thus, for the purpose of our analyses we excluded subjects with MCI or dementia (n=240), without *APOE* genotype data available (n=141), and without cognitive status data available (n=6). We further excluded 27 participants who did not belong to any of the three basic ethnic groups, thus, the final sample consisted of 1,944 WHICAP participants, all aged 65 years or older.

Ethics Statement

Ethics approval was obtained for the specific study. Written informed consent for the study was obtained from all participants and/or their authorized representatives and study partners. Institutional review boards (IRB) were constituted according to applicable state and federal requirements for the study. WHICAP has been approved by the IRB of the New York State Psychiatric Institute.

Dementia diagnosis

In order to define the medical/cognitive status of the participants, each of them underwent a structured in-person interview including an assessment of health and function, as well as a neuropsychological assessment. The diagnosis of mild cognitive impairment (MCI) and dementia was based on standard research criteria, using all available information at a consensus conference consisting of physicians, neurologists, neuropsychologists, and psychiatrists [27]. For the diagnosis of probable or possible AD, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [28, 29] were used.

Sleep measures

Sleep quality was assessed using the Sleep Scale from the RAND Medical Outcomes Study. This scale is a self-report 12-item questionnaire [30, 31]. Each of the questions has a possible rating of 0–6, based on the frequency of the sleep problem. Using the sleep questionnaire manual [31], we used the five clustered sleep categories to define our analyses phenotype: 1. Sleep disturbance, 2. Snoring, 3. Sleep short of breath/awaking with a headache, 4. Sleep adequacy, and 5. Daytime somnolence. Additionally, categories 2 and 3 were combined into a single variable 'sleep apnea'. The final score for each sleep category was calculated by adding up the values of each of the component questions (Data in brief 1). We reversed the scores of the sleep questions so that responses were consistent with a higher score indicating greater sleep dysfunction.

APOE genotyping

WHICAP participants were *APOE* genotyped as previously described [32]. *APOE* genotypes were transformed into a dichotomous trait based on the number of *APOE*-ε4 alleles: 0 if the individual does not carry any copy of the ε4 allele (non-ε4 carriers) or 1 if the individual carries 1 or 2 copies of the ε4 allele (ε4 carriers). The above definition was based on the existing literature which mentions that in Alzheimer's disease –and other neurodegenerative diseases as well-, the effect of *APOE*-ε4 is additive and having two copies of the ε4 allele lowers significantly the age at onset of the disease, in contrast to people with one or none of the ε4 allele [33]. Carriers of ε2ε4 alleles were not included in the initial sample due to the opposite effect of these two alleles [34–36] (data in brief 2).

Statistical analysis

All statistical analyses were performed using SPSS 22 (SPSS, Chicago, Illinois). Nominally significant p values were defined as $p < 0.05$.

Unadjusted Linear Regression Analyses

We used linear regression models with *APOE*-ε4 at baseline evaluation as the predictor and the previously described sleep score as the independent variable.

Adjusted Linear Regression Analyses

Secondary analyses were performed adjusting for: age, sex, ethnicity, education, and body mass index (BMI). Ethnicity was ascertained based on self-report using the format of the 1990 census [6]. Participants were then assigned to one of the three groups: White, African-American, and Caribbean-Hispanic.

To further examine any possible differences among the ethnic groups, we stratified the sample and perform analyses within each ethnic group independently (Whites n= 431, African Americans n=465, and Caribbean-Hispanics n=1,048).

Results

The mean age of the study participants was 79 (± 7) years. There was a higher percentage of females (68.6%) and a higher frequency of participants with Caribbean-Hispanic ancestry (53.2%). Regarding to *APOE* gene, 24.9% of the individuals were *APOE*-ε4 carriers (Table 1).

Results in the unadjusted model showed that *APOE*-ε4 carriers present with lower levels of snoring (β=−0.02, SE= 0.01, p =0.010) and sleep apnea (β=−0.01, SE= 0.01, p =0.037) compared to non-ε4 carriers (Table 2). After adjusting for all the covariates, the association remains unchanged for both snoring (β=−0.02, SE=0.01, p=0.006) and sleep apnea (β= −0.01, SE= 0.01 p=0.018) (Table 2).

After stratifying the analyses by ethnicity, our results suggest that *APOE*-ε4 carriers with Caribbean-Hispanic ethnicity are less likely to have problems in snoring (p=0.004), compared to the other two ethnic groups (Data in Brief 3).

None of the other sleep variables was significantly associated with *APOE*-ε4 (see Table 2).

Discussion

The current study examined the relationship between *APOE*-ε4 and self-reported sleep disturbances, in a large, and ethnically diverse sample of non-demented older adults. Our results suggest that compared to subjects with no copies of *APOE*-ε4 allele, carriers of the *APOE*-ε4 allele showed decreased problems in snoring and sleep apnea.

This is the first study that has reported a positive association between *APOE*-ε4 and sleep, specifically snoring/sleep apnea. Existing literature has reported the potential protective effect of *APOE-ε4* in many different disorders [37, 38]. Furthermore, *APOE*-ε4 may also determine if anti-hypertensive ACE inhibitor drugs are effective in protecting the brain from aging and dementia [39].

While this may appear counter intuitive, we suggest a plausible explanation for the specific association. It has been shown that *APOE*-ε4 has a positive association with higher levels of vitamin D [40]. A separate study reports an association between vitamin d deficiency and larger tonsil size [41]. Furthermore, tonsillar enlargement, even mild cases, has been associated significantly with the pathogenesis of OSA [42]. If we consider this information together in light of our findings, we may infer that *APOE*-ε4 carriers may have less snoring problems because of the positive advantage incurred by the *APOE*-ε4 in promoting higher vitamin D levels, and thus minimizing snoring. Further research measuring the levels of vitamin d –which, in the present study were not available-, could shed more light on the above association.

Based on our results, Caribbean-Hispanic subjects carrying the *APOE*-ε4 allele are less likely to have increased problems in snoring compared to the two other ethnic groups. However, research examining the association between sleep and ethnicity has been scarce and the results of other studies have been inconsistent [43–45]. We did not find a significant

statistical interaction between *APOE*-ε4 and ethnicity suggesting that the large sample size of Caribbean-Hispanics in our sample (n=1,048), when compared to non-Caribbean-Hispanics (n=896), may explain the results. Further longitudinal research including the same number of participants within each ethnic group would provide more information about the role that ethnicity plays in the association between *APOE*-ε4 and snoring/sleep apnea.

Like many other phenotypes, sleep is complex in etiology [(46)], with most likely multiple environmental and genetic causes [(47)]. Genetic research in human complex phenotypes has demonstrated that one of the most predominant genetic patterns for complex phenotypes is that of many loci [(48)], individually with small effects on phenotype. To assess the clinical relevance, future research need to focus on integrate small-modest genetic effects from multiple candidate genes and potential environmental factors.

The present study has some limitations. The subjective nature of the sleep measurements may have biased our results and future studies should consider a more specific diagnostic tool to measure sleep disturbances such as actigraphy. Additionally, we cannot exclude the possibility that genetic variants other than *APOE*-ε4, along with environmental factors, might contribute to snoring and sleep apnea variability.

The present study has also some significant strengths. To the best of our knowledge, this is the first study to assess the role of *APOE* locus in sleep disturbances using such a large multi-ethnic cohort of non-demented elderly participants. Furthermore, the detailed neurological and neuropsychological assessment of the WHICAP participants permitted an accurate assessment of their cognitive status.

The current study suggests that when compared to *APOE*-ε4 non carriers, *APOE*-ε4 carriers show decreased snoring and/or sleep apnea over and above possible confounders. Further research is necessary in order to examine the biological mechanisms underlying the role of *APOE*-ε4 gene in sleep's pattern.

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Highlights

- *APOE*-ε4 is associated with decreased snoring in the elderly.
- *APOE*-ε4 is also associated with decreased sleep apnea.
- Caribbean-Hispanic *APOE*-ε4 carriers have decreased problems in snoring.

Table 1

Demographic characteristics of the APOE-ε4 carriers and non-ε4 carries.

Characteristics	*APOE*-ε4 carriers	*APOE*-ε4 non-carriers	Total
Age at visit (years), Mean(SD)	79 (6.6)	80 (6.7)	80 (6.7)
Education (years), Mean(SD)	10 (5.1)	10 (5.0)	10 (5.0)
Gender, N (%)			
Female	340 (70.2)	997 (68.3)	1337 (68.8)
Male	144 (29.8)	463 (31.7)	607 (31.2)
Ethnicity, N (%)			
White	86 (17.8)	345 (23.6)	431 (22.2)
African-American	168 (34.7)	297 (20.3)	465 (23.9)
Caribbean-Hispanic	230 (47.5)	818 (56.0)	1048 (53.9)
BMI, Mean(SD)	28.63 (5.6)	29.03 (5.5)	28.93 (5.5)
Total, N (%)	484 (24.9)	1460 (75.1)	1944 (100)

Table 2

Results from the association analyses between APOE-ε4 and sleep variables.

Sleep variable	Correlation with *APOE*-ε4							
	Unadjusted Model				Adjusted Model			
	B	**SE**	**Beta**	***p* value**	**B**	**SE**	**Beta**	***p* value**
Sleep disturbance	−0.00	0.00	−0.024	0.210	−0.00	0.00	−0.842	0.400
Snoring	−0.02	0.01	−0.059	**0.010**	−0.02	0.01	−0.067	**0.006**
Sleep short of breath/w headache	0.01	0.01	0.009	0.598	0.00	0.01	0.005	0.833
Sleep adequacy	0.00	0.00	0.009	0.892	−0.00	0.00	−0.241	0.810
Daytime somnolence	−0.00	0.00	−0.030	0.192	−0.00	0.00	−0.003	0.410
Sleep apnea	−0.01	0.01	−0.047	**0.037**	−0.01	0.01	−0.057	**0.018**

A *p* value < 0.05 was considered nominally significant, and the corresponding results are shown in bold. Adjustments were made for: age, sex, ethnicity, education, and BMI.