Association Between Apolipoprotein E ϵ4 and Sleep-Disordered Breathing in Adults

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Context Apolipoprotein E ϵ4 (*ApoE ϵ4*) is a well-known risk factor for Alzheimer disease and cardiovascular disease. Sleep-disordered breathing occurs in Alzheimer disease patients and increases risks for cardiovascular disease. Complex interactions among sleep, brain pathology, and cardiovascular disease may occur in *ApoE ϵ4* carriers.

Objective To study whether genetic variation at the level of *ApoE* is associated with sleep-disordered breathing or sleep abnormalities in the general population.

Design, Setting, and Participants Ongoing longitudinal cohort study of sleep disorders at a US university beginning in 1989, providing a population-based probability sample of 791 middle-aged adults (mean [SD] age, 49 [8] years; range, 32-68 years).

Main Outcome Measure Nocturnal polysomnography to evaluate apnea-hypopnea index.

Results The probability of moderate-to-severe sleep-disordered breathing (apnea-hypopnea index ≥15%) was significantly higher in participants with ϵ*4*, independent of age, sex, body mass index, and ethnicity (12.0% vs 7.0%; *P*=.003). Mean (SEM) apnea-hypopnea index was also significantly higher in participants with *ApoE ϵ4* (6.5 [0.6] vs 4.8 [0.3]; *P*=.01). These effects increased with the number of *ApoE ϵ4* alleles carried.

Conclusions A significant portion of sleep-disordered breathing is associated with *ApoE ϵ4* in the general population.

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SLEEP-DISORDERED BREATHING (SDB) is prevalent but largely undiagnosed in adults.[1] Persons with SDB are at increased risk for hypertension[2,3] and have increased cardiovascular disease (CVD) morbidity and mortality.[4] Characteristics of SDB, including changes in sleep architecture and electroencephalogram (EEG) slowing, are also present in persons with Alzheimer disease (AD).[5,6] Apolipoprotein E (ApoE), a protein involved in lipid metabolism, has 3 major allelic variants: ϵ2, ϵ3, and ϵ*4*. While a protective effect for AD may be conferred by the *ApoE* ϵ2 allele, risks for CVD and AD are increased by the *ApoE* ϵ*4* allele.[7,8] In this study, we assessed the contribution of ApoE genetic variation to SDB, sleep architecture, and other sleep parameters.

METHODS

Data were obtained from participants in an ongoing longitudinal cohort study of sleep disorders that began in 1989.[3] The cohort was constructed with a 2-stage probability sampling procedure on a random sample of employed men and women to maximize variability in SDB.[1,9] Every 4 years, participants underwent overnight polysomnography, blood sampling, and other tests. Informed consent was obtained in writing, using forms approved by the University of Wisconsin institutional review committee.

Studies involving participants who had fewer than 5 hours of polysomnographically documented sleep or who used psychotropic drugs were excluded (n=558 studies). A total of 1344 overnight studies in 791 participants (up to 3 studies per participant) were included.

Sleep architecture and episodes of apnea and hypopnea were determined with standard in-laboratory polysomnography that included electroencephalography (EEG), electro-oculography, electromyelography, oximetry to detect arterial oxyhemoglobin saturation, thermistry and nasal pressure to detect airflow, and respiratory inductance plethysmography to record rib cage and abdominal excursions of breathing. Each 30-second epoch of the polysomnographic records was visually inspected and scored by trained technicians for sleep stage, apnea (≥10 seconds with no breathing), and hypopnea (a discernible reduction in the amplitude of respiratory inductance plethysmography associated with a ≥4% reduction in oxyhemoglobin saturation). The average number of apneas and hypopneas per

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hour of sleep (apnea-hypopnea index [AHI])[3] was used as the summary measure of SDB. An EEG-slowing index (ratio of slow [delta and theta] to fast [alpha and beta] frequencies in eyes-closed, awake C3/A2 EEG) was calculated using fast Fourier spectral analysis[6] on a subset of sleep studies with an adequate duration of quiet awake measurement (n=381). Apolipoprotein E genotype was determined using the polymerase chain reaction–restriction fragment length polymorphism method.[10] Serum cholesterol, triglyceride, and glucose levels were also measured.

Statistical techniques for data with repeated measures were used for our data of up to 3 studies per participant on factors with intraparticipant variation, including sleep architecture, AHI, and biochemical markers (SAS 8.0 software, SAS Institute, Cary, NC). Statistical analyses included repeated measures analysis of covariance regression for continuous outcomes (SAS PROC MIXED) and logistic regression for binary outcomes using the generalized estimating equations approach for repeated measures (SAS PROC GENMOD). Regression analyses were adjusted for potential confounding variables and for correlated observations within participants for multiple sleep studies. A binary outcome (AHI ≥15) was used to indicate clinically significant sleep apnea.

RESULTS

Allele frequencies for *ApoE* ϵ*2*, ϵ*3*, and ϵ*4* were 0.07, 0.78, and 0.15, respectively. Low-density lipoprotein (LDL) and triglycerides were increased while high-density lipoprotein (HDL) was decreased in ϵ*4*-positive vs ϵ*4*-negative participants (TABLE 1). Mean (SEM) total cholesterol and LDL were both decreased in ϵ*2*-positive vs ϵ*2*-negative participants (total cholesterol: 194 [3] mg/dL vs 206 [1] mg/dL, $P<.001$; LDL: 117 [3] mg/dL vs 131 [1] mg/dL, $P<.001$) (to convert mg/dL to mmol/L, multiply values by 0.0259). None of the other parameters differed between ϵ*2*-positive and ϵ*2*-negative participants (data not shown). A significant association between ϵ*4* and SDB was found. The prevalence of elevated (≥15) AHI and mean AHI were both significantly increased in ϵ*4*-positive participants independent of age, sex, BMI, and ethnicity (Table 1 and TABLE 2). This association was present in both sexes (data not shown) and more pronounced in the 14 *ApoE* ϵ*4* homozygous participants of the cohort (24 sleep studies) (Table 2). Sleep architecture, EEG slowing (untransformed and log transformed) did not differ with *ApoE* ϵ*4* status (Table 1).

COMMENT

Our results indicate that *ApoE* ϵ*4* is associated with sleep apnea. We also found that *ApoE* ϵ*2* is associated with lower levels of total and LDL cholesterol while ϵ*4* is associated with higher levels of LDL and triglycerides, as previously reported.[7] Sleep-disturbed breathing has been reported to cluster in families[11,12] and ϵ*4* might be 1 of the multiple genetic factors involved in susceptibility to this syndrome. Of note, SDB prevalence increases with aging,[1,13] and our sample is that of middle-aged adults. We found a substantial effect of ϵ*4* on SDB: there was a 2-fold increase in the odds of SDB (Table 2) in ϵ*4*-positive vs ϵ*4*-negative participants. Considering the prevalence of the ϵ*4* polymorphism (15%), up to 8% of AHI (15) in the general population might be caused by the effects of ϵ*4*.

Only 1 study has examined the effect of ϵ*4* on SDB.[14] In that study, participants with sleep apnea were more likely

Table 1. Sleep Parameters and Biochemical Markers in Participants*

Variable	*ApoE* ϵ*4*–Negative (n = 569)	*ApoE* ϵ*4*–Positive (n = 222)	*P* Value
Sample characteristics†			
Studies, No.	960	384	
Men, %	56	64	.07
Age, mean (SD), y	49 (8)	49 (9)	.56
White, %	97	96	.89
BMI, mean (SD), kg/m^2	30 (6)	30 (6)	.81
Current smoker, %	17	15	.33
Hypertension, %	33	33	.96
Sleep parameters†			
Sleep architecture			
Sleep latency, mean (SE), min	9.2 (0.3)	9.3 (0.5)	.88
REM latency, mean (SE), min	110 (2)	115 (3)	.19
Sleep efficiency, % (SE)	86.3 (0.3)	87.0 (0.4)	.16
Stage 1, % (SE)	9.1 (0.2)	9.6 (0.3)	.24
Stage 2, % (SE)	59.4 (0.3)	60.1 (0.5)	.26
Stage 3 and 4, % (SE)	12.5 (0.3)	11.7 (0.5)	.20
REM, % (SE)	18.9 (0.2)	18.5 (0.3)	.37
Other sleep parameters†			
AHI ≥15, %	7.0	12.0	.003
AHI, mean (SE)	4.8 (0.3)	6.5 (0.6)	.01‡
EEG slowing index, mean (SE)§	0.80 (0.05)	0.71 (0.07)	.27
Biochemical markers, mean (SE), mg/dL‖			
Total cholesterol	203 (2)	209 (3)	.07
LDL	128 (1)	135 (3)	.02
HDL	48 (1)	44 (1)	.001
Triglycerides	139 (4)	162 (9)	.01
Glucose	98 (1)	97 (1)	.73

*ApoE indicates apolipoprotein E; BMI, body mass index; REM, rapid eye movement; AHI, apnea-hypopnea index; EEG, electroencephalogram; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.
†Participants had 1, 2, or 3 studies. Data adjusted for multiple studies on some participants.
‡Calculated for log (AHI + 1).
§Data adjusted for multiple studies on some participants and were calculated on a subset of 161 *ApoE* ϵ*4*–negative and 70 ApoE ϵ–positive subjects (252 and 112 studies, respectively).
‖Data adjusted for multiple studies on some participants. Calculated for a subset of 513 to 516 *ApoE* ϵ*4*–negative and 194 to 199 *ApoE* ϵ*4*–positive subjects (628 to 632 and 229 to 238 studies, respectively). To convert mg/dL to mmol/L for total, LDL, and HDL cholesterol, multiply values by 0.0259; for triglycerides, multiply by 0.0113; and for glucose, multiply by 0.0555.

Table 2. Effects of the *ApoE ϵ4* Genotype on Sleep-Disordered Breathing*

	ApoE ϵ4–Negative (n = 569)	*ApoE ϵ4*–Positive (n = 222)	*P* Value†	No. of *ϵ4* Alleles 0 (n = 569)	1 (n = 208)	2 (n = 14)	*P* for Trend†
Sleep studies, No.‡	960	384		960	360	24	
AHI index							
Mean (SEM)	4.8 (0.3)	6.5 (0.6)	.01§	4.8 (0.3)	6.2 (0.6)	10.5 (3.5)	.003§
Median (range)	1.3 (0-121)	2.0 (0-81)		1.3 (0-121)	2.0 (0-81)	3.6 (0-54)	
Adjusted mean (SEM)‖	5.2 (0.6)	6.7 (0.9)	.01§	5.2 (0.6)	6.4 (0.8)	10.9 (4.5)	.03
OR (95% CI) for AHI ≥15		2.0 (1.2-3.5)	.01		2.1 (1.2-3.2)	3.9 (1.5-9.9)	.005

*ApoE indicates apolipoprotein E; AHI, apnea-hypopnea index; OR, odds ratio; and CI, confidence interval.
†Corrected for multiple measurements for some participants.
‡Participants had 1, 2, or 3 studies.
§Calculated for log (AHI + 1).
‖Adjusted for *ϵ2*, age, sex, body mass index, smoking, hypertension, and ethnicity.

to be *ϵ4* homozygotes than were controls, but the difference was not statistically significant. The controls were mostly middle-aged men who had not been studied for SDB. Up to 9% of middle-aged men in the general population have an AHI of 15 or more,[1] so it is likely that the control group contained men with SDB, which would underestimate the association of *ϵ4* and SDB. Our study is unique because every participant has undergone nocturnal polysomnography, with most having been studied several times.

Another report suggests significant interactions among sleep, AD, and the *ϵ4* genotype, with a higher risk of AD morbidity present in *ϵ4*-positive participants who napped for more than 60 min/d.[15] Sleep-disordered breathing causes daytime sleepiness and prolonged napping. Thus, increased SDB in *ϵ4*-positive participants might be responsible, at least partially, for this interaction.

Our finding is a simple statistical association that does not indicate a causal relationship between ApoE *ϵ4* and sleep apnea. A complex syndrome, SDB involves the central control of breathing and peripheral predisposing factors, leading to anatomical narrowing and collapse of the upper airway during sleep. Thus, SDB frequently occurs after such brain injuries as head trauma[16] and stroke,[17] demonstrating the importance of central factors. On the other hand, *ϵ4* may increase the density of β-amyloid deposits and neurofibrillary tangles in nondemented individuals.[7,8] Increased pathology in sleep/respiratory centers might contribute to centrally mediated SDB in *ϵ4*-positive participants. Additional studies are needed to extend these findings.

The increased SDB prevalence in *ϵ4*-positive participants may have clinical consequences. The established cardiovascular impact of SDB and the deleterious effect of *ϵ4* on lipid metabolism may have synergistic effects. Sleep-disordered breathing and *ϵ4* could also interact centrally to impair cognition. Not only may *ϵ4* predispose to neurodegenerative changes, but also SDB induces sleepiness and may damage the brain irreversibly through long-term hypoxemia.[18,19] Further studies will be needed to confirm and extend these findings.

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REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993; 328:1230-1235.
2. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378-1384.
3. Nieto FJ, Young TB, Lind BK, et al, for the Sleep Heart Health Study. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *JAMA*. 2000;283:1829-1836.
4. Young T, Peppard P. Sleep-disordered breathing and cardiovascular disease: epidemiologic evidence for a relationship. *Sleep*. 2000;23(suppl 4):S122-S126.
5. Prinz PN, Peskind ER, Vitaliano PP, et al. Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. *J Am Geriatr Soc*. 1982;30:86-93.
6. Petit D, Lorrain D, Gauthier S, Montplaisir J. Regional spectral analysis of the REM sleep EEG in mild to moderate Alzheimer's disease. *Neurobiol Aging*. 1993;14:141-145.
7. Siest G, Pillot T, Regis-Bailly A, et al. Apolipoprotein E: an important gene and protein to follow in laboratory medicine. *Clin Chem*. 1995;41:1068-1086.
8. Mahley RW, Huang Y. Apolipoprotein E: from atherosclerosis to Alzheimer's disease and beyond. *Curr Opin Lipidol*. 1999;10:207-217.
9. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000;284:3015-3021.
10. Murphy GM Jr, Taylor J, Kraemer HC, et al. No association between apolipoprotein E ϵ 4 allele and rate of decline in Alzheimer's disease. *Am J Psychiatry*. 1997; 154:603-608.
11. Guilleminault C, Partinen M, Hollman K, et al. Familial aggregates in obstructive sleep apnea syndrome. *Chest*. 1995;107:1545-1551.
12. Redline S, Tishler PV, Tosteson TD, et al. The familial aggregation of obstructive sleep apnea. *Am J Respir Crit Care Med*. 1995;151:682-687.
13. Redline S, Tishler PV, Hans MG, et al. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. *Am J Respir Crit Care Med*. 1997;155:186-192.
14. Saarelainen S, Lehtimaki T, Kallonen E, et al. No relation between apolipoprotein E alleles and obstructive sleep apnea. *Clin Genet*. 1998;53:147-148.
15. Asada T, Motonaga T, Yamagata Z, et al. Associations between retrospectively recalled napping behavior and later development of Alzheimer's disease. *Sleep*. 2000;23:629-634.
16. Guilleminault C, Yuen KM, Gulevich MG, et al. Hypersomnia after head-neck trauma: a medicolegal dilemma. *Neurology*. 2000;54:653-659.
17. Bassetti C, Aldrich MS. Sleep apnea in acute cerebrovascular diseases. *Sleep*. 1999;22:217-223.
18. Montplaisir J, Bedard MA, Richer F, Rouleau I. Neurobehavioral manifestations in obstructive sleep apnea syndrome before and after treatment with continuous positive airway pressure. *Sleep*. 1992;15:S17-S19.
19. Engleman HM, Kingshott RN, Martin SE, Douglas NJ. Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). *Sleep*. 2000;23(suppl 4):S102-S108.