# Greater Cognitive Deficits with Sleep-Disordered Breathing among Individuals with Genetic Susceptibility to Alzheimer's Disease: the Multi-Ethnic Study of Atherosclerosis

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Running title: Sleep-Disordered Breathing and Cognition

Conception and Design: DJ, RW, ID, AF, SR, LC, SR; Analysis and interpretation: DJ, JL, RW, MR, ID, AF, SR, LC, RO, RS, SR; Drafting or critically revising the manuscript: DJ, JL, RW, MR, ID, AF, SR, LC, RO, RS, SR

Acknowledgements: MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-000040, UL1-TR-001079, UL1-TR-001881, and DK06349. Funding for SHARe genotyping was provided by NHLBI Contract N02-HL-64278. Genotyping was performed at Affymetrix (Santa Clara, California, USA) and the Broad Institute of Harvard and MIT (Boston, Massachusetts, USA) using the Affymetrix Genome-Wide Human SNP Array 6.0. Funding support for the Sleep Polysomnography dataset was provided by grant HL56984. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Descriptor code: 15.9; Word count: 4,035

At a Glance Commentary: Although sleep apnea has been implicated as a cause of cognitive dysfunction, community-based studies and randomized controlled studies have shown conflicting findings, possibly due to inconsistencies in the measurement of sleep exposures and heterogeneity of the study samples. We investigated indicators of sleep-disordered breathing and various cognitive domains. Our results showed that overnight hypoxemia and self-reported sleepiness were associated with cognition dysfunction. Associations were strongest in individuals with the APOE-ε4 risk allele, suggesting heterogeneity in risk of sleep-disturbance related cognitive impairment may arise due to inter-individual differences in genetic susceptibility to Alzheimer's disease.

## Abstract

**Rationale**: There are conflicting findings regarding the link between sleep apnea and cognitive dysfunction.
**Objective**: Investigate associations between indicators of sleep-disordered breathing (SDB) and cognitive function in the Multi-Ethnic Study of Atherosclerosis and assess effect modification by the apolipoprotein ε-4 (APOE-ε4) allele.
**Methods:** A diverse population (N=1,752) underwent Type 2 in-home polysomnography, which included measurement of % sleep time <90% oxyhemoglobin saturation (%Sat<90%) and apnea-hypopnea index (AHI). Epworth Sleepiness Scale score (ESS) and sleep apnea syndrome (SAS; AHI $\geq$ 5 and ESS> 10) were also analyzed. Cognitive outcomes included the Cognitive Abilities Screening Instrument (CASI); Digit Symbol Coding Test (DSC); and Digit Span Tests (DST) Forward and Backward.
**Measurements and Main Results:** Participants were 45.4% male, age 68.1(standard deviation: 9.1) years with a median AHI=9.0 and mean ESS=6.0. Approximately, 9.7% had SAS and 26.8% had at least one copy of the APOε4 allele. In adjusted analyses, a one standard deviation increase in %Sat<90% and ESS score were associated with a poorer attention and memory assessed by the DST Forward score (β=-0.12 (standard error: 0.06) and β=-0.13 (0.06), respectively; $P \leq 0.05$). SAS and higher ESS scores were also associated with poorer attention and processing speed as measured by the DSC, β=-0.69 (0.35) and β=-1.42 (0.35), respectively ($P<0.05$). The presence of APOE-ε4 allele modified the associations of %Sat<90% with DST forward and of ESS with DSCT, $P_{interaction} \leq 0.05$.
**Conclusions:** Overnight hypoxemia and sleepiness were associated with cognition. The average effect estimates were small, similar to effects estimated for several other individual dementia risk factors. Associations were strongest in APOE-ε4 risk allele carriers. Our results: 1) suggest that SDB be considered among a group of modifiable dementia risk factors; and 2) highlight the potential vulnerability of APOE-ε4 risk allele carriers with SDB.

Word count: 286


Keywords: Sleep Apnea, Hypoxemia, Sleepiness, Cognition, Apolipoprotein ε-4

## Introduction

Sleep-disordered breathing (SDB) is a highly prevalent condition that is characterized by repeated pauses (apneas or hypopneas) in breathing during sleep.[1] SDB is particularly prevalent among elderly populations, older men and racial minority groups (African American, Hispanic, Asian).[2–4] Individuals with SDB commonly report problems with cognition and may be at increased risk for dementia.[5]

SDB is associated with hypoxemia, sleep fragmentation, and cerebral vascular disease, which may directly affect brain function, and adversely affect cognition, as well as may indirectly lead to cognitive impairment via impairments in attention and executive function due to sleepiness.[6] Results of meta-analyses demonstrate that there is strong evidence supporting the influence of SDB on attention, vigilance, memory (verbal immediate recall, delayed long-term visual and verbal recall, verbal learning), executive function, and visuospatial/constructional abilities.[7,8] However, clinical and epidemiological studies as well as randomized control trials (RCT) have reported mixed results regarding the association between SDB, or SDB treatment, and cogniton.[7–18] Although a number of reports have shown that the apnea-hypopnea index (AHI) and overnight hypoxemia are associated with cognitive deficits using a variety of performance tests,[8,14,19–23] other studies have not.[16,17,24–26] In the largest clinical trial to date evaluating the role of SDB treatment on cognitive outcomes, the Apnea Positive Pressure Long-term Efficacy Study, primary analyses found no significant improvements in cognitive function with positive airway pressure (PAP) use among participants with sleep apnea, although small improvements were observed among severe patients in a secondary analysis.[27] The 6-month intervention period may have been too short to demonstrate significant improvements; the adherence with PAP may have been inadequate for full response; and the participant enrollment biased toward less impaired subjects. Additionally, studies have shown improvements in subdomains of executive function with CPAP use.[18] Overall, the prior studies on SDB and cognition have shown conflicting results, possibly due to heterogeneity in populations studied, including disease severity or differences in underlying susceptibility as well as the measurement of sleep disturbances and cognitive test batteries. The selection of cognitive tests has varied and some of the traditional tests used in neuropsychology batteries do not have assessment of a sleep-dependent effect. In particular, there may be subgroups of individuals who may be more vulnerable to the deleterious effects of SDB on cognition due to genetic or other susceptibities.[28]

Genetic factors may influence susceptibility to cognitive deficits resulting from SDB-related stresses. In particular, the apolipoprotein epsilon 4 allele (APOE-ε4), found in 20% of the general population, is associated with a significantly increased risk for Alzheimer's Disease (AD) and possibly SDB. [29–32] It is hypothesized that carriers of the APOE-ε4 allele have a limited response to physiological challenges which increase vulnerability to cognitive deficits,[33] and SDB specifically, by augmenting inflammation, may potentiate neuroinflammatory processes associated with APOE-ε4. Nikodemova and colleagues found that SDB (AHI $\geq$ 15) was associated with poorer performance among APOE-ε4 positive individuals who were employed in Wisconsin.[28] In a cohort of older women, the AHI was more strongly associated with cognitive function in carriers of at least one APOE-ε4 allele relative to individuals without the allele.[34] Lastly, in a sample of 36 community-dwelling older adults, higher levels of AHI were associated with lower memory scores among those with the APOE-ε4 allele only.[35] Although the results of these studies have important implications for older adults, they were based on predominantly white populations and should be replicated in more diverse samples.

We examined the relation between several measures of SDB obtained by polysomnography and standardized sleep questionnaires and cognitive function in a diverse sub-sample of middle-aged to older adults participating in the Multi-Ethnic Study of Atherosclerosis, (MESA). We also assessed whether the association was modified by presence of the APOE-ε4 risk allele.

## Methods

MESA is a longitudinal study of 6,814 non-Hispanic white, African American, Hispanic and Chinese adults recruited between 2000-2002 when they were between 45-84 years old, and free of known cardiovascular disease. Participants were recruited from six communities, in the United States (US) including Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. The study was designed to prospectively investigate risk factors for the development of subclinical cardiovascular disease and its progression to clinical disease.[36] Additional details on the study design for MESA have been previously published.[36] The current analyses used data from the MESA Sleep and MESA Cognition ancillary studies conducted with the 5th MESA follow-up examination.

*Sleep Measures*

Between 2010-2013, MESA participants who did not report regular use of oral devices, nocturnal oxygen, or nightly positive airway pressure devices were invited to participate in the MESA Sleep Ancillary Study.[37] MESA participants (N=2,060) agreed to participate and underwent in-home polysomnography (PSG) using a 15-channel monitor (Compumedics Somte ® System; Compumedics Ltd., Abbotsville, AU). Sleep data were centrally scored[37] and provided quantitative assessments of levels of overnight hypoxemia, apneas and hypopneas, arousal indices, and sleep architecture (including total sleep time, and sleep stage distributions).

Our primary exposure variables are apnea-hypopnea index (AHI), % sleep time <90% oxyhemoglobin saturation (%Sat<90%), sleep apnea syndrome (SAS) and Epworth Sleepiness Scale (ESS) score. AHI was calculated as the average number of all apneas plus hypopneas associated with a 4% desaturation per hour of sleep. Given the older age of the cohort and interest in moderate or more severe disease, SDB was defined as an AHI≥15 events/hour. SAS was defined as having an AHI ≥5 plus an ESS score >10.[38] The ESS score assessed excessive daytime sleepiness using 8 scenarios, scored on a 4-Likert scale from 0 to 3, with the score ranging from 0 to 24.

Other sleep measures that were assessed were AHI in rapid eye movement (REM) sleep, AHI in non-rapid eye movement (NREM) sleep, sleep duration (total sleep time), and sleep efficiency (the proportion of time spent asleep between sleep onset and lights on), all derived from PSG. Sleep duration and sleep efficiency was also assessed from actigraphy using the Actiwatch Spectrum wrist actigraph (Philips Respironics, Murrysville, PA). Participants wore the actigraph on the nondominant wrist for 7 consecutive days.

*MESA Cognitive Battery*

MESA participants were administered three validated neuropsychological tests at the 5th follow-up exam for MESA. Examinations were administered in English, Spanish and Mandarin Chinese by centrally trained and certified examiners. The test battery was designed to assess several cognitive domains including global cognitive function, processing speed, and working memory.[39]

The Cognitive Abilities Screening Instrument (CASI) is a measure of global cognitive function developed for use across cultures.[40] The CASI consists of 25 items representing the following cognitive abilities: attention, concentration, orientation, short-term memory, long-term memory, language, visual construction, verbal fluency, and abstraction/judgment. Items were summed to provide an overall cognitive function score ranging from 0-100.

The Digit Symbol-Coding (DSC) test is a subtest of the Wechsler Adult Intelligence Scale-III and measures attention and how quickly simple perceptual or mental operations can be performed.[41] A series of nine simple symbols (e.g., +, >) paired with numbers (numerals 1-9) are presented in a legend at the top of the page. Participants copy the correct symbol into an empty box directly below another box containing one of the randomly ordered numbers. The score (range: 0-133) is the number of correctly copied symbols in 120 seconds, with higher values indicating better performance.

The Digit Span Test (DST) is a subtest of the Wechsler Adult Intelligence Scale-III,[41] and measures attention and working memory. The DST contains two measures-the Forward and Backward. For the DST Forward, participants are asked to repeat back spans of numbers read to them by the trained examiner. For every correctly recalled span, a point is awarded (scores ranging from 0 to 14). For DST Backward spans are repeated in reverse order with scores ranging from 0 to 14. DST subtests test are related but different cognitive functions[42]. DST Forward performance reflects attention and concentration while DS-Backward is more sensitive to elements of executive control and visuospatial processing.[39,43]

*Genetic Effect Modifier*

APOE-ε4 isoforms were estimated from single nucleotide polymorphisms (SNPS) rs7412 and rs429358 from genotyping conducted using an Applied Biosystems TaqMan SNP system (ABI# C_904973_10 and C_3084793_20, respectively). In a quality control comparison, APOE-ε4 isoforms showed excellent agreement (κ=0.965) with genotyped results in a MESA substudy that directly genotyped the APOE-ε4 alleles. Participants with at least one ε4 allele were classified as having the APOE-ε4 allele.

*Covariates*

We also considered race, age, body mass index (BMI), education level, smoking status, hypertension, diabetes, benzodiazepine use, and depressive symptoms as potential confounders and adjusted for these variables in analyses. Height and weight were measured and BMI ($kg/m^2$)

was calculated. Education level was ascertained using an 8-level scale, and was further classified as less than high school, high school or graduate education diploma (GED), some college and college degree or higher. Gross family income was self-reported within categories including <$25,000, $25-$49,999, $50-$74,999 and ≥$75,000. Smoking status was self-reported and categorized as current or never/former smoker. Participants with elevated systolic or diastolic blood pressure (≥ 130/85 mmHg based on direct measurements or reported use of antihypertensive medications) were classified as hypertensive. Participants with a fasting glucose ≥ 126 mg/dL or taking insulin or oral diabetes medication were considered diabetic. Benzodiazepine use was self-reported by participants. Participants completed the Center for Epidemiologic Studies Depression Scale (CES-D) for a measure of depressive symptoms.

*Statistical Analysis*

For descriptive purposes, we compared the characteristics and cognitive test values of the study sample by SDB status (AHI>15) using chi-square and t-tests for categorical and continuous measures, respectively. A series of linear regression models were fit to examine the association between each sleep exposure and cognitive function scores. Measures were modeled continuously, and log-transformations were used for CASI due to its skewed distribution. Associations were modeled in units of change in standard deviation (SD) for each sleep measure to facilitate comparisons. We used a sequential modeling approach with model 1 adjusting for age, sex, race, education; model 2 further adjusting for diabetes, hypertension, and smoking; model 3 further adjusting for actigraphy-based sleep duration and sleep efficiency; and model 4 further adjusting for ESS score. We found no evidence of confounding by benzodiazepine and depressive symptoms, however, in sensitivity analyses; we further adjusted for benzodiazepine use and depressive symptoms based on *a priori* knowledge that these variables are likely confounders of the association between sleep and cognition.

To examine effect modification, we included an interaction term between sleep exposures and APOE-ε4 in separate models using model 2 covariates. Stratified analyses were presented using forest plots. Interactions were considered significant based on a *P* value of <0.10.

**Results**

A total of 1,752 individuals had data available for both PSG and cognitive tests. The sample had a mean age of 68.1 (standard deviation=9.1) years; 37.1% were non-Hispanic white with the remaining African American (26.3%) , Hispanic (24.6%) or Asian American (12.0%), and 54.6% were female. Compared to the MESA Exam 5 participants, individuals in this analysis were slightly younger, had a higher BMI and a higher proportion of Asian and Hispanic participants. There were no differences based on sex. Approximately 33.4% of the study sample met criteria for moderate or more severe SDB (AHI≥15) and 9.7% met the definition of SAS. The median AHI, %Sat<90, and ESS were 9.0, 0.65, and 5.0, respectively. The prevalence of the APOE-ε4 allele was 26.8%.

Individuals with SDB were more likely to be male, older, obese, and less physically active relative to those without SDB, *P*<0.01 (Table 1). SDB groups also varied by race, *P*≤0.10, and education level *P*≤0.05. Higher education was associated with better cognition scores across all domains (P≤0.01). In unadjusted analyses, scores for CASI and DST Forward and Backward did not differ by SDB classification (Table 2). The unadjusted DSC score was higher among individuals without SDB compared to those with SDB, P<0.01.

Higher levels of overnight hypoxemia and daytime sleepiness were associated with small estimated decrements in attention and concentration (DST Forward) performance after adjustment for demographic and education status (*P's* <0.05) (Table 3). Associations were slightly attenuated in fully adjusted analyses but remained statistically significant. Similarly, SAS and higher sleepiness scores were associated with small decements in attention and poorer processing speed (DSC) after adjustment for demographic and education status (*P's* <0.05). The association persisted in fully adjusted models. No other associations between sleep parameters and cognitive function were significant.

In sensitivity analyses, we further adjusted for benzodiazepine use and depressive symptoms, and all associations remained and parameter estimates were similar except for the association between daytime sleepiness and DST Forward. Adjusting for depressive symptoms attenuated the association between daytime sleepiness and DST Forward (β=-0.09 (0.06)).

*Effect Modification (Figure 1)*

APOE-ε4 modified the association between %Sat<90% and DST Forward and between the ESS and DSC ($P_{interaction}$ ≤0.05). In stratified analyses, among those with the ε4 allele, more severe overnight hypoxemia was associated with a poorer DST Forward score (β=-0.37 (0.12), *P*<0.01). In contrast, no association was observed between hypoxemia and DST Forward scores among those individuals without the risk allele (β=-0.03 (0.08), *P*=0.68). Additionally, the association between sleepiness scores and poorer DSC scores were twice as strong in individuals with the presence of APOE-ε4 genotype as opposed to those without, β=-2.40 (0.63), *P*<0.01, β=-0.91 (0.43), *P*<0.05, respectively. There were no interactions between AHI or SAS and APOE-ε4.

## Discussion

Among an ethnically and socioeconomically diverse population of middle-age to older individuals, we found that sleep-related hypoxemia and daytime sleepiness were cross-sectionally associated with cognitive dysfunction, particularly tasks related to attention and concentration, but not with a test of global cognitive function or working memory. The AHI was not associated with any cognitive tests in this study. Moreover, we found evidence that the associations between SDB and cognition varied by APOE-ε4. Specifically, we found that APOE-ε4 carriers showed poorer attention and concentration as hypoxemia increased. Similarly, they showed poorer attention and slower processing speed as daytime sleepiness increased. Overall, these results suggest: a) overnight hypoxemia and self-reported sleepiness are more closely associated with cognitive function than the AHI; b) associations with sleepiness persisted even after adjusting for sleep duration and sleep efficiency, suggesting that sleepiness may be a marker of SDB-related cognitive vulnerability; c) the most sensitive of our measures of cognitive impairment was the DST Forward, a measure of attention and concentration; d) a genetic vulnerability to AD modified the key associations.

Prior studies have been inconsistent regarding the association between sleep-disordered breathing and cognitive function, perhaps due to population heterogeneity (with underlying differences in susceptibility to SDB-related changes in cognitive function), level of severity of SDB among samples studied, and differences in methods and measures employed, including the range of cognitive assessments administered and cognitive domains assessed. Our findings are generally consistent with prior research that has reported that the severity of hypoxemia was related to poorer cognitive performance.[13,14,20,22,34,44] Hypoxemia is thought to contribute to neurologic dysfunction through several pathways, including triggering of cellular events leading to apoptosis of hippocampal cells.[45] Cerebral vascular damage also may result from hypoxemia related chemoreflex activation, sympathetic vasoconstriction, and nocturnal blood pressure surges.[46,47] Intermittent hypoxemia influences both oxidative stress and inflammation, which can result in cognitive deficits by inducing neuronal cell loss within specific regions of the brain that lead to deficits.[48]

We also observed significant associations between daytime sleepiness and cognition, and showed that these associations persisted after adjusting for sleep duration and sleep efficiency. These findings are consistent with the research of Cohen-Zion and colleagues, who found that increases in daytime sleepiness were associated with decreased cognitive performance.[17] Similarly, among two separate adult populations, excessive daytime sleepiness was also associated with increased risk of cognitive impairment; and the authors suggest that daytime sleepiness could be a marker for cognitive decline.[49,50] Reduced alertness resulting from sleepiness has been shown to decrease brain activity and function.[51] Although cognitive deficits may be directly due to sleepiness (and reduced vigilance), sleepiness also may provide an integrative measure of the effects of multiple sleep disrupting exposures that may contribute to cognitive decline, serving as a marker that identifies those most vulnerable to SDB.[52] Although sleepiness is not specific to SDB, our associations persisted after adjusting for both sleep duration and sleep efficiency, suggesting that insufficient sleep was not an explanation for our results. Results were slightly attenuated when adjusting for depressive symptoms, and underscore the possibility that altered mood also may be a marker or mediator of cognitive changes occurring with SDB. Sleep disturbance, fatigue and difficulty concentrating are cardinal features of depression.[53]

Notably, the AHI was not associated with cognitive outcomes. Although the AHI is a standard clinical metric, there is increasing recognition that this measure has a number of limitations and does not provide specific information regarding physiological disturbances (e.g., may reflect different degrees of arousal and patterns of breathing and sleep disruptions). Recent studies of cognitive function in children also have shown no associations between the AHI and a comprehensive and sensitive cognitive battery, but showed associations between sleepiness, or Sleep Apnea Syndrome (defined by a mildly elevated AHI and elevated ESS score) and cognition.[54] Further, current definitions of AHI allow for significant variation in level of hypoxemia across patients, and a 3 or 4% decrease in oxygen desaturation can result in levels of oxyhemoglobin that are still well within normal ranges and not indicative of hypoxemia. Our results suggest the clinical assessment of sleepiness may be useful in identifying patients at increased risk for cognitive deficits associated with SDB.

The MESA cognitive battery was chosen to provide an assessment of cognitive performance across several domains. We found that our sleep measures were mostly related to tests of attention, concentration, and short-term memory, cognitive domains also observed to be impacted in other studies of patients with SDB.[13,15,19] Of all tests, the DST Forward was most consistently associated with sleepiness and hypoxemia. In contrast, a more cognitively challenging test, Digit Span Backwards, was not. One explanation for this seemingly counter intuitive finding is that tasks that are more demanding may result in greater cognitive activation, and help recruit compensatory mechanisms that overcome attentional deficits.[55] Neuroimaging studies provide evidence for such compensatory cognitive activation, particularly in the middle-age to older adulthood age-range,[56] and compensatory cerebral activation during cognitive processing has been documented in APOE-ε4 carriers.[57] Since DST Backward is more difficult than DST Forward, participants may have increased their effort in the conduct of DST Backward.

However, it is also important to note that DST Backward and DST Forward measure overlapping but different cognitive functions.[58] DST Backward is well documented to capture cognitive control and executive functioning processes, while DST Forward is considered to be a measure of attention and short-term memory that does not place high demands on executive processes such as sequencing and planning. While some studies have observed a negative impact of SDB on a broad range of executive function tasks, including both DST Forward and DST Backward,[59] similar to our own observation, others find a negative impact on DST Forward but not DST Backward suggesting SDB impacts attention and short-term memory.[60] Also, among e4 carriers, SDB is most consistently observed to negatively impact memory tasks.[28,61]

It is noteworthy that associations were not observed between sleep measures and a test of overall cognitive measure of cognition, the CASI, which may lack sufficient sensitivity. Characteristics of our cohort, a middle-aged, male and female, and community sample may have attenuated the associations. It is also possible that residual confounding was present in associations with the CASI where cultural differences may be involved despite our adjustments in models. We did not observe an association of memory function and hypoxemia on the CASI, but the memory component only consists of recall of three words, which may not have been sufficiently sensitive to hypoxemia-associated memory impairment. Further, unlike older, clinic samples where patients are often concerned about cognitive function, our sample was not selective for either sleep related health or cognitive problems.

There is growing recognition that there is large population variability in susceptibility to various exposures, which has stimulated the emergence of "precision medicine." An important finding of our work is the observed effect modification by APOE-ε4. Notably, APOE-ε4 carriers had stronger associations between hypoxemia and attention/concentration as well as between sleepiness and processing speed. Our findings are consistent with several studies.[28,34,62,63] Data from the Wisconsin Sleep Cohort, showed an association between AHI and memory and executive function in carriers of the APOE-ε4 allele; however other measures of SDB were not assessed.[28] In a sample of older women, AHI, central apnea index, and oxygen saturation nadir less than 90% were associated with a higher risk of cognitive impairment among APOE-ε4 carriers.[34] In our diverse cohort, we found that those with the risk allele appeared more vulnerable to the influence of overnight hypoxemia and sleepiness on attention, memory and processing speed than those without a risk allele. These associations are plausible given that SDB-related hypoxemia and oxidative stress most negatively impacts brain function in individuals genetically susceptible to synaptic degeneration.

It is noteworthy that other studies have observed lower performance on the Digit Span and DSC Tests to be predictive of cognitive decline and conversion to Mild Cognitive Impairment (MCI), as well as conversion from MCI to Alzheimer's Disease. Kurt and colleagues, found that lower digit span performance in older adults with subjective memory complaints predicted future neuropsychological test performance indicative of MCI.[64] In a larger cohort of 148 elderly adults with MCI, performance on the DSC was one of the strongest predictors of time to convert to Alzheimer's Disease.[65] MCI encompasses a range of cognitive deficits, some of which may present before others.[66] SDB-associated performance deficits in digit span measures of attention, speed of processing and working memory may be the first to capture subtle cognitive impairments that are indicative of subsequent MCI and dementia. While longitudinal studies are required to more fully investigate this possibility, the clinical implications are substantial. Along with APOE-ε4 risk allele status, MCI status is one of the most robust risk factors for the development of dementia.

Given the current lack of effective treatments for AD and dementia there is a significant focus on secondary prevention, with recent research supporting the value in targeting multiple modifiable risk factors.[67–69] Although each risk factor may individually have small effect, indices that include multiple behavioral, lifestyle and somatic risk factors together may account for as much as 50% of the excessive risk for dementia.[68,69] The association of SDB with dementia,[13,14] and poorer performance on cognitive function measures, suggest that SDB represents an additional modifiable risk factor to reduce the risk of conversion from typical aging to MCI, and from MCI to dementia. Although our average effect estimates for SDB indices were small, they were significant even after adjustment for traditional risk factors such as age, hypertension and diabetes.

This study contributes to the literature in several additional ways. We analyzed indices of SDB with three well-standardized neuropsychological tests. Standardized polysomnography allowed us to adjust for objective measures of sleep duration and sleep efficiency. Our study cohort was ethnically and racially diverse, providing greater generalizability than prior studies. Genetic data allowed us to test for effect modification. Despite these strengths, our study also has limitations. Although we included several sleep measures, these were derived from a single night of PSG, which does not capture variation over time. It is possible that duration of SDB and age of onset are important factors in influencing cognitive function. Our analyses were cross-sectional which does not allow us to infer causality. Lastly, it is possible that more sensitive cognitive tests would have yielded different results. Given the correlation among exposures and outcomes, we did not adjust for multiple comparisons.

*Conclusion*

Cognitive impairment is highly prevalent among elderly populations, and is associated with increased disability, neuropsychiatric symptoms and health care costs.[70–72] Our results suggest that more severe overnight hypoxemia and sleepiness may be related to poorer cognitive function, especially attention, concentration, and process speed in middle-aged to older adults, and that the risk is greater among carriers of the APOE-ε4 alleles, a known risk factor for Alzheimer's disease. With use of this type of information, future risk stratification may help to identify individuals at increased risk for SDB-related cognitive deficits and target those individuals for studies evaluating the impact of treatment or prevention.

**Table 1.** Study Population Characteristics by Sleep-Disordered Breathing (N=1752)

| Characteristic | Sleep-Disordered Breathing (AHI≥15) Yes (n=585) Mean (SD) or No. (%) | Sleep-Disordered Breathing (AHI≥15) No (n=1167) Mean (SD) or No. (%) | *P*-Value* |
|---|---|---|---|
| Age, y | 68.6 (8.8) | 67.9 (9.2) | 0.11 |
| Male | 356 (60.8) | 440 (37.7) | <0.001 |
| Education | | | 0.05 |
| <HS | 94 (16.1) | 156 (13.4) | |
| HS or GED | 86 (14.7) | 203 (17.4) | |
| Some College | 156 (26.7) | 262 (22.5) | |
| ≥College | 249 (42.6) | 543 (46.6) | |
| Income | | | |
| <$25,000 | 175 (30.5) | 289 (25.4) | 0.16 |
| $25-$49,999 | 144 (25.1) | 309 (27.1) | |
| $50-$74,999 | 95 (16.6) | 205 (18.0) | |
| ≥$75,000 | 159 (27.7) | 336 (29.5) | |
| Race/Ethnicity | | | 0.10 |
| Non-Hispanic White | 197 (33.7) | 453 (38.8) | |
| Chinese | 79 (13.5) | 131 (11.2) | |
| African American | 152 (26.0) | 309 (26.5) | |
| Hispanic | 157 (26.8) | 274 (23.5) | |
| Body Mass Index | 30.5 (5.8) | 27.6 (5.1) | <0.001 |
| COPD | 11 (1.9) | 23 (2.0) | 0.90 |
| Depressive Symptoms | 8.0 (7.1) | 8.1 (7.8) | 0.83 |
| Antidepressant use | 3 (0.5) | 15 (1.3) | 0.13 |
| Benzodiazepine use | 14 (2.4) | 66 (5.6) | 0.002 |
| Current Smoker | 32 (5.5) | 87 (7.5) | 0.12 |
| Physical Activity, h per day | 9.0 (5.9) | 9.6 (6.1) | 0.05 |

| | | | |
|---|---|---|---|
| Total Sleep Time[a], min | 392.5 (75.3) | 387.7 (83.7) | 0.23 |
| Sleep Efficiency[a] | 89.9 (3.6) | 89.8 (3.8) | 0.65 |
| % REM[b] | 16.6 (6.9) | 19.1 (6.1) | <0.001 |
| % Slow Wave Sleep[b] | 8.4 (8.2) | 10.9 (9.2) | <0.001 |
| AHI, median (IQR) [b] | 32.2 (19.4-41.2) | 5.6 (2.0-9.0) | <0.001 |
| Arousal Index[b] | 29.5 (13.2) | 18.4 (8.9) | <0.001 |
| % Time Oxyhemoglobin Saturation <90%[b], median (IQR) | 8.2 (1.6-9.4) | 1.6 (0.0-0.97) | <0.001 |
| Sleep Apnea Syndrome | 97 (16.8) | 71 (6.2) | <0.001 |
| Epworth Sleepiness Scale | 6.4 (4.3) | 5.8 (3.9) | 0.01 |
| APOE-ε4 allele | 150 (26.7) | 297 (26.8) | |

IQR=Interquartile range; *chi-square or ANOVA tests for categorical or continuous variables (respectively); [a]Measures are based on actigraphy; [b]Measures are based on in-home polysomnography.

**Table 2.** Unadjusted Values (Mean, SD) of Cognitive Function Tests by Sleep-Disordered Breathing

| Cognitive Function | SDB | No SDB |
|---|---|---|
| CASI[c] | 87.6 (8.2) | 88.3 (8.4) |
| DSC[a] | 49.8 (18.2) | 53.0 (18.7) |
| Digit Span Forward | 9.5 (2.8) | 9.6 (2.8) |
| Digit Span Backward[c] | 5.5 (2.3) | 5.7 (2.4) |

CASI-Cognitive Abilities Screening Instrument (version 2); DSC-Digit Symbol Coding; [a]*P*<0.01, [b]*P*<0.05, [c]*P*<0.10

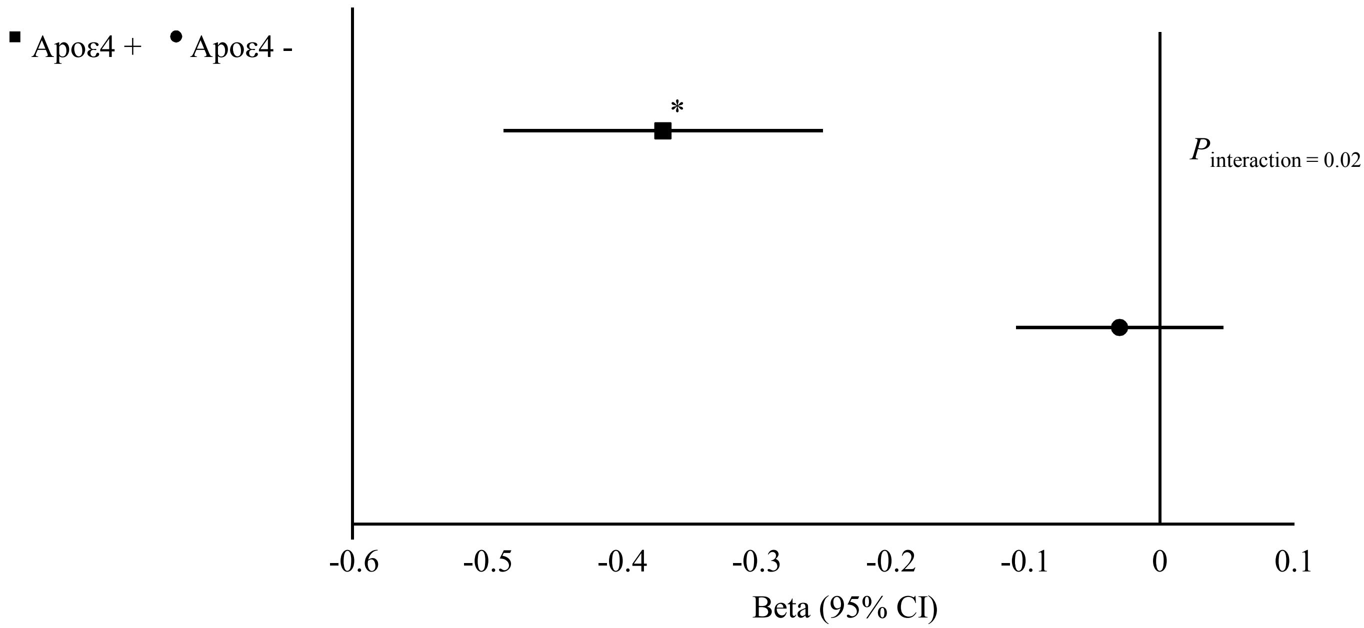
**Table 3.** Regression Analysis of Sleep-Disordered Breathing Indices and Cognitive Function, N=1752.

| | **CASI** | | | | **DSC** | | | | **DST Forward** | | | | **DST Backward** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| AHI | 0.0004 (0.0023) | 0.0004 (0.0023) | 0.0005 (0.0023) | 0.0004 (0.0023) | -0.140 (0.354) | -0.016 (0.353) | -0.035 (0.354) | 0.089 (0.355) | 0.020 (0.064) | 0.032 (0.065) | 0.041 (0.066) | 0.064 (0.066) | -0.003 (0.053) | 0.017 (0.053) | 0.012 (0.054) | 0.015 (0.054) |
| % Saturation <90% | 0.004 (0.002)[c] | 0.004 (0.002)[c] | 0.004 (0.002)[c] | 0.004 (0.002)[c] | -0.693 (0.344) | -0.447 (0.341) | -0.428 (0.341) | -0.295 (0.341) | **-0.151 (0.063)[b]** | **-0.137 (0.063)[b]** | **-0.138 (0.063)[b]** | **-0.123 (0.063)[b]** | -0.027 (0.051) | -0.014 (0.052) | -0.011 (0.052) | -0.007 (0.052) |
| SAS | 0.001 (0.002) | 0.001 (0.002) | 0.001 (0.002) | ------ | **-0.903 (0.345)[a]** | **-0.698 (0.344)[b]** | **-0.694 (0.346)[b]** | ------ | -0.066 (0.062) | -0.056 (0.064) | -0.062 (0.064) | ----- | -0.011 (0.052) | -0.004 (0.052) | -0.002 (0.052) | ------ |
| ESS | 0.0005 (0.0022) | 0.0001 (0.0023) | 0.0003 (0.0023) | ------ | **-1.55 (0.345)[a]** | **-1.43 (0.344)[a]** | **-1.42 (0.346)[a]** | ------ | **-0.148 (0.063)[b]** | **-0.127 (0.064)[b]** | **-0.132 (0.064)[b]** | ----- | -0.035 (0.052) | -0.019 (0.052) | -0.014 (0.053) | ------ |

Model 1: Adjusted for age, sex, race, education level
Model 2: Model 1 + age, sex, race, education level, diabetes, hypertension, smoking
Model 3: Model 2 + sleep duration, sleep efficiency
Model 4: Model 3 + sleepiness
[a]*P*<0.01, [b]*P*<0.05, [c]*P*<0.10
Estimates are standardized
Shown are beta coefficients and standard errors

**Figure 1.**

**A.**




**B.**

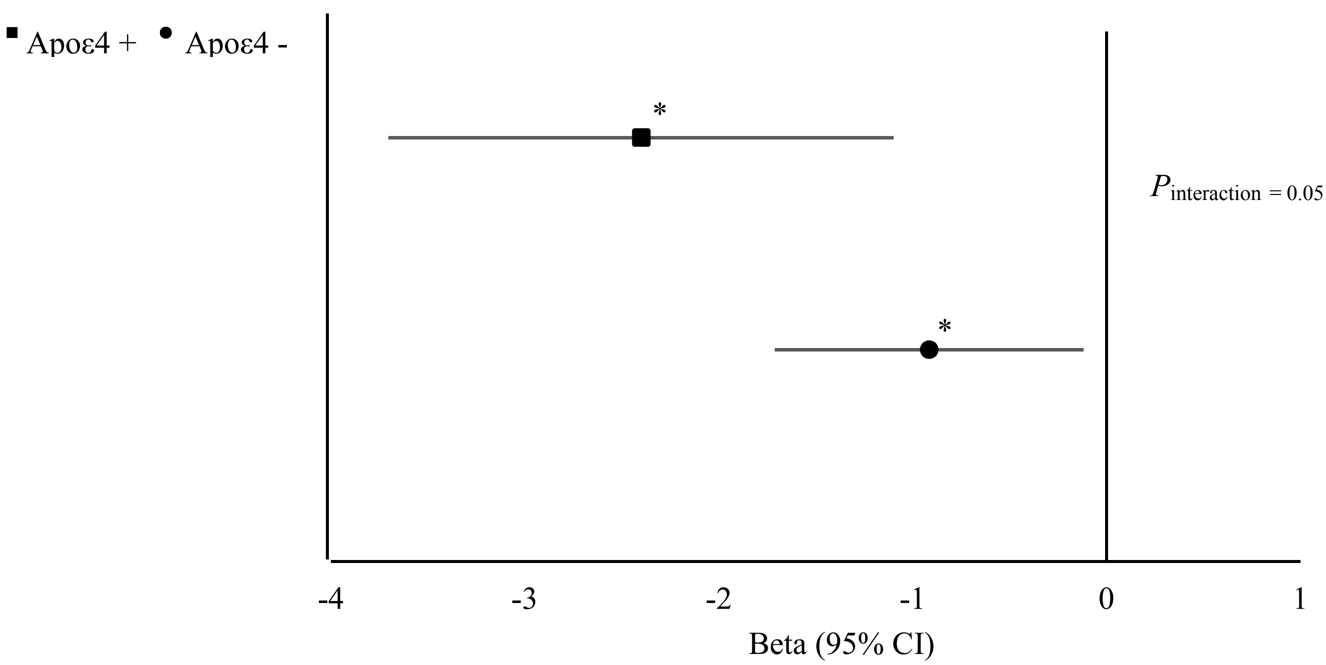



Figure 1illustrates forest plots showing the association between indices of SDB and cognitive tests by APOε4 risk allele. The data presented are the associations between sleep indices and cognitive outcome stratified by APOε4. (A) % Saturation <90% and Digit Span Forward Test by APOε4. (B) Epworth Sleepiness Scale and Digit Symbol Coding Test by APOε4.*$P$<0.05

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# Greater Cognitive Deficits with Sleep-Disordered Breathing among Individuals with Genetic Susceptibility to Alzheimer's Disease: the Multi-Ethnic Study of Atherosclerosis

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Running title: Sleep-Disordered Breathing and Cognition

Conception and Design: DJ, RW, ID, AF, SR, LC, SR; Analysis and interpretation: DJ, JL, RW, MR, ID, AF, SR, LC, RO, RS, SR; Drafting or critically revising the manuscript: DJ, JL, RW, MR, ID, AF, SR, LC, RO, RS, SR

Acknowledgements: MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-000040, UL1-TR-001079, UL1-TR-001881, and DK06349. Funding for SHARe genotyping was provided by NHLBI Contract N02-HL-64278. Genotyping was performed at Affymetrix (Santa Clara, California, USA) and the Broad Institute of Harvard and MIT (Boston, Massachusetts, USA) using the Affymetrix Genome-Wide Human SNP Array 6.0. Funding support for the Sleep Polysomnography dataset was provided by grant HL56984. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Descriptor code: 15.9; Word count: 4,035

At a Glance Commentary: Although sleep apnea has been implicated as a cause of cognitive dysfunction, community-based studies and randomized controlled studies have shown conflicting findings, possibly due to inconsistencies in the measurement of sleep exposures and heterogeneity of the study samples. We investigated indicators of sleep-disordered breathing and various cognitive domains. Our results showed that overnight hypoxemia and self-reported sleepiness were associated with cognition dysfunction. Associations were strongest in individuals with the APOE-ε4 risk allele, suggesting heterogeneity in risk of sleep-disturbance related cognitive impairment may arise due to inter-individual differences in genetic susceptibility to Alzheimer’s disease.

**Abstract**

**Rationale**: There are conflicting findings regarding the link between sleep apnea and cognitive dysfunction.

**Objective**: Investigate associations between indicators of sleep-disordered breathing (SDB) and cognitive function in the Multi-Ethnic Study of Atherosclerosis and assess effect modification by the apolipoprotein ε-4 (APOE-ε4) allele.

**Methods:** A diverse population (N=1,752) underwent Type 2 in-home polysomnography, which included measurement of % sleep time <90% oxyhemoglobin saturation (%Sat<90%) and apnea-hypopnea index (AHI). Epworth Sleepiness Scale score (ESS) and sleep apnea syndrome (SAS; AHI $\geq$ 5 and ESS> 10) were also analyzed. Cognitive outcomes included the Cognitive Abilities Screening Instrument (CASI); Digit Symbol Coding Test (DSC); and Digit Span Tests (DST) Forward and Backward.

**Measurements and Main Results:** Participants were 45.4% male, age 68.1(standard deviation: 9.1) years with a median AHI=9.0 and~~,~~ mean ESS=6.0. ~~;~~ Approximately, 9.7% had SAS and 26.8% had at least one copy of the APOε4 allele. In adjusted analyses, ~~A~~a one standard deviation increase in %Sat<90% and ESS score were associated with a poorer attention and memory assessed by the DST Forward score (β=-0.12 (standard error: 0.06) and β=-0.13 (0.06), respectively; $P \leq 0.05$). SAS and higher ESS scores were also associated with poorer attention and processing speed as measured by the DSC, β=-0.69 (0.35) and β=-1.42 (0.35), respectively ($P<0.05$). The presence of APOE-ε4 allele modified the associations of ~~-~~%Sat<90% with DST forward and of ESS with DSCT, $P_{interaction}<0.05$.

**Conclusions:** Overnight hypoxemia and sleepiness were associated with cognition. The average effect estimates were small, similar to effects estimated for several other individual dementia risk factors. Associations were strongest in APOE-ε4 risk allele carriers. Our results: 1) suggest that SDB be considered among a group of modifiable dementia risk factors; and 2) highlight the potential vulnerability ~~-~~of APOE-ε4 risk allele carriers with SDB.

Word count: 286

Keywords: Sleep Apnea, Hypoxemia, Sleepiness, Cognition, Apolipoprotein ε-4

## Introduction

Sleep-disordered breathing (SDB) is a highly prevalent condition that is characterized by repeated pauses (apneas or hypopneas) in breathing during sleep.[1] SDB is particularly prevalent among elderly populations, older men and racial minority groups (African American, Hispanic, Asian).[2–4] Individuals with SDB commonly report problems with cognition and may be at increased risk for dementia.[5]

SDB is associated with hypoxemia, sleep fragmentation, and cerebral vascular disease, which may directly affect brain function, and adversely affect cognition, as well as may indirectly lead to cognitive impairment via impairments in attention and executive function due to sleepiness.[6] Results of meta-analyses demonstrate that there is strong evidence supporting the influence of SDB on attention, vigilance, memory (verbal immediate recall, delayed long-term visual and verbal recall, verbal learning), executive function, and visuospatial/constructional abilities.[7,8] However, clinical and epidemiological studies as well as randomized control trials (RCT) have reported mixed results regarding the association between SDB, or SDB treatment, and cogniton.[7–18] Although a number of reports have shown that the apnea-hypopnea index (AHI) and overnight hypoxemia are associated with cognitive deficits using a variety of performance tests,[8,14,19–23] other studies have not.[16,17,24–26] In the largest clinical trial to date evaluating the role of SDB treatment on cognitive outcomes, the Apnea Positive Pressure Long-term Efficacy Study, primary analyses found no significant improvements in cognitive function with positive airway pressure (PAP) use among participants with sleep apnea, although small improvements were observed among severe patients in a secondary analysis.[27] The 6-month intervention period may have been too short to demonstrate significant improvements; the adherence with PAP may have been inadequate for full response; and the participant enrollment biased toward less impaired subjects. Additionally, studies have shown improvements in subdomains of executive function with CPAP use.[18] Overall, the prior studies on SDB and cognition have shown conflicting results, possibly due to heterogeneity in populations studied, including disease severity or differences in underlying susceptibility as well as the measurement of sleep disturbances and cognitive test batteries. The selection of cognitive tests hasve varied and some of the traditional tests used in neuropsychology batteries do not have assessment of a sleep-dependent effect. In particular, there may be subgroups of individuals who may be more vulnerable to the deleterious effects of SDB on cognition due to genetic or other susceptibities.[28]

Genetic factors may influence susceptibility to cognitive deficits resulting from SDB-related stresses. In particular, the apolipoprotein epsilon 4 allele (APOE-ε4), found in 20% of the general population, is associated with a significantly increased risk for Alzheimer's Disease (AD) and possibly SDB. [29–32] It is hypothesized that carriers of the APOE-ε4 allele have a limited response to physiological challenges which increase vulnerability to cognitive deficits,[33] and SDB specifically, by augmenting inflammation, may potentiate neuroinflammatory processes associated with APOE-ε4. Nikodemova and colleagues found that SDB (AHI $\geq$ 15) was associated with poorer performance among APOE-ε4 positive individuals who were employed in Wisconsin.[28] In a cohort of older women, the AHI was more strongly associated with cognitive function in carriers of at least one APOE-ε4 allele relative to individuals without the allele.[34] Lastly, in a sample of 36 community-dwelling older adults, higher levels of AHI were associated with lower memory scores among those with the APOE-ε4 allele only.[35] Although the results of these studies have important implications for older adults, they were based on predominantly white populations and should be replicated in more diverse samples.

We examined the relation between several measures of SDB obtained by polysomnography and standardized sleep questionnaires and cognitive function in a diverse sub-sample of middle-aged to older adults participating in the Multi-Ethnic Study of Atherosclerosis, (MESA). We also assessed whether the association was modified by presence of the APOE-ε4 risk allele.

**Methods**

MESA is a longitudinal study of 6,814 non-Hispanic white, African American, Hispanic and Chinese adults recruited between 2000-2002 when they were between 45-84 years old, and free of known cardiovascular disease. Participants were recruited from six communities, in the United States (US) including Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. The study was designed to prospectively investigate risk factors for the development of subclinical cardiovascular disease and its progression to clinical disease.[36] Additional details on the study design for MESA have been previously published.[36] The current analyses used data from the MESA Sleep and MESA Cognition ancillary studies conducted with the 5th MESA follow-up examination.

*Sleep Measures*

Between 2010-2013, MESA participants who did not report regular use of oral devices, nocturnal oxygen, or nightly positive airway pressure devices were invited to participate in the MESA Sleep Ancillary Study.[37] MESA participants (N=2,060) agreed to participate and underwent in-home polysomnography (PSG) using a 15-channel monitor (Compumedics Somte ® System; Compumedics Ltd., Abbotsville, AU). Sleep data were centrally scored[37] and provided quantitative assessments of levels of overnight hypoxemia, apneas and hypopneas, arousal indices, and sleep architecture (including total sleep time, and sleep stage distributions).

Our primary exposure variables are apnea-hypopnea index (AHI), % sleep time <90% oxyhemoglobin saturation (%Sat<90%), sleep apnea syndrome (SAS) and Epworth Sleepiness Scale (ESS) score. AHI was calculated as the average number of all apneas plus hypopneas associated with a 4% desaturation per hour of sleep. Given the older age of the cohort and interest in moderate or more severe disease, SDB was defined as an AHI≥15 events/hour. SAS was defined as having an AHI ≥5 plus an ESS score >10.[38] The ESS score assessed excessive daytime sleepiness using 8 scenarios, scored on a 4-Likert scale from 0 to 3, with the score ranging from 0 to 24.

Other sleep measures that were assessed were AHI in rapid eye movement (REM) sleep, AHI in non-rapid eye movement (NREM) sleep, sleep duration (total sleep time), and sleep efficiency (the proportion of time spent asleep between sleep onset and lights on), all derived from PSG. Sleep duration and sleep efficiency was also assessed from actigraphy using the Actiwatch Spectrum wrist actigraph (Philips Respironics, Murrysville, PA). Participants wore the actigraph on the nondominant wrist for 7 consecutive days.

*MESA Cognitive Battery*

MESA participants were administered three validated neuropsychological tests at the 5th follow-up exam for MESA. Examinations were administered in English, Spanish and Mandarin Chinese by centrally trained and certified examiners. The test battery was designed to assess several cognitive domains including global cognitive function, processing speed, and working memory.[39]

The Cognitive Abilities Screening Instrument (CASI) is a measure of global cognitive function developed for use across cultures.[40] The CASI consists of 25 items representing the following cognitive abilities: attention, concentration, orientation, short-term memory, long-term memory, language, visual construction, verbal fluency, and abstraction/judgment. Items were summed to provide an overall cognitive function score ranging from 0-100.

The Digit Symbol-Coding (DSC) test is a subtest of the Wechsler Adult Intelligence Scale-III and measures attention and how quickly simple perceptual or mental operations can be performed.[41] A series of nine simple symbols (e.g., +, >) paired with numbers (numerals 1-9) are presented in a legend at the top of the page. Participants ~~move~~ copy the correct symbol into an empty box directly below another box containing one of the randomly ordered numbers. The score (range: 0-133) is the number of correctly copied symbols in 120 seconds, with higher values indicating better performance.

The Digit Span Test (DST) is a subtest of the Wechsler Adult Intelligence Scale-III,[41] and measures attention and working memory. The DST contains two measures-the Forward and Backward. For the DST Forward, participants are asked to repeat back spans of numbers read to them by the trained examiner. For every correctly recalled span, a point is awarded (scores ranging from 0 to 14). For DST Backward spans are repeated in reverse order with scores ranging from 0 to 14. DST subtests test are related but different cognitive functions[42]. DST Forward performance reflects attention and concentration while DS-Backward is more sensitive to elements of executive control and visuospatial processing.[39,43]

*Genetic Effect Modifier*

APOE-ε4 isoforms were estimated from single nucleotide polymorphisms (SNPS) rs7412 and rs429358 from genotyping conducted using an Applied Biosystems TaqMan SNP system (ABI# C_904973_10 and C_3084793_20, respectively). In a quality control comparison, APOE-ε4 isoforms showed excellent agreement (κ=0.965) with genotyped results in a MESA substudy that directly genotyped the APOE-ε4 alleles. Participants with at least one ε4 allele were classified as having the APOE-ε4 allele.

*Covariates*

We also considered race, age, body mass index (BMI), education level, smoking status, hypertension, diabetes, benzodiazepine use, and depressive symptoms as potential confounders and adjusted for these variables in analyses. Height and weight were measured and BMI ($kg/m^2$)

was calculated. Education level was ascertained using an 8-level scale, and was further classified as less than high school, high school or graduate education diploma (GED), some college and college degree or higher. Gross family income was self-reported within categories including <$25,000, $25-$49,999, $50-$74,999 and ≥$75,000. Smoking status was self-reported and categorized as current or never/former smoker. Participants with elevated systolic or diastolic blood pressure (≥ 130/85 mmHg based on direct measurements or reported use of antihypertensive medications) were classified as hypertensive. Participants with a fasting glucose ≥ 126 mg/dL or taking insulin or oral diabetes medication were considered diabetic. Benzodiazepine use was self-reported by participants. Participants completed the Center for Epidemiologic Studies Depression Scale (CES-D) for a measure of depressive symptoms.

*Statistical Analysis*

For descriptive purposes, we compared the characteristics and cognitive test values of the study sample by SDB status (AHI>15) using chi-square and t-tests for categorical and continuous measures, respectively. A series of linear regression models were fit to examine the association between each sleep exposure and cognitive function scores. Measures were modeled continuously, and log-transformations were used for CASI due to its skewed distribution. Associations were modeled in units of change in standard deviation (SD) for each sleep measure to facilitate comparisons. We used a sequential modeling approach with model 1 adjusting for age, sex, race, education; model 2 further adjusting for diabetes, hypertension, and smoking; model 3 further adjusting for actigraphy-based sleep duration and sleep efficiency; and model 4 further adjusting for ESS score. We found no evidence of confounding by benzodiazepine and depressive symptoms, however, in sensitivity analyses; we further adjusted for benzodiazepine use and depressive symptoms based on *a priori* knowledge that these variables are likely confounders of the association between sleep and cognition.

To examine effect modification, we included an interaction term between sleep exposures and APOE-ε4 in separate models using model 2 covariates. Stratified analyses were presented using forest plots. Interactions were considered significant based on a *P* value of <0.10.

**Results**

A total of 1,752 individuals had data available for both PSG and cognitive tests. The sample had a mean age of 68.1 (standard deviation=9.1) years; 37.1% were non-Hispanic white with the remaining African American (26.3%) , Hispanic (24.6%) or Asian American (12.0%), and 54.6% were female. Compared to the MESA Exam 5 participants, individuals in this analysis were slightly younger, had a higher BMI and a higher proportion of Asian and Hispanic participants. There were no differences based on sex. Approximately 33.4% of the study sample met criteria for moderate or more severe SDB (AHI≥15) and 9.7% met the definition of SAS. The median AHI, %Sat<90, and ESS were 9.0, 0.65, and 5.0, respectively. The prevalence of the APOE-ε4 allele was 26.8%.

Individuals with SDB were more likely to be male, older, obese, and less physically active relative to those without SDB, *P*<0.01 (Table 1). SDB groups also varied by race, *P*≤0.10, and education level *P*≤0.05. Higher education was associated with better cognition scores across all domains (P≤0.01). In unadjusted analyses, scores for CASI and DST Forward and Backward did not differ by SDB classification (Table 2). The unadjusted DSC score was higher among individuals without SDB compared to those with SDB, P<0.01.

Higher levels of overnight hypoxemia and daytime sleepiness were associated with small estimated decrements in ~~poorer working memory~~attention and concentration (DST Forward) performance after adjustment for demographic and education status (*P's* <0.05) (Table 3). Associations were slightly attenuated in fully adjusted analyses but remained statistically significant. Similarly, SAS and higher sleepiness scores were associated with small decements in attention and poorer processing speed (DSC) after adjustment for demographic and education status (*P's* <0.05). The association persisted in fully adjusted models. No other associations between sleep parameters and cognitive function were significant.

In sensitivity analyses, we further adjusted for benzodiazepine use and depressive symptoms, and all associations remained and parameter estimates were similar except for the association between daytime sleepiness and DST Forward. Adjusting for depressive symptoms attenuated the association between daytime sleepiness and DST Forward (β=-0.09 (0.06)).

*Effect Modification (Figure 1)*

APOE-ε4 modified the association between %Sat<90% and DST Forward and between the ESS and DSC ($P_{interaction} \leq 0.05$). In stratified analyses, among those with the ε4 allele, more severe overnight hypoxemia was associated with a poorer DST Forward score (β=-0.37 (0.12), *P*<0.01). In contrast, no association was observed between hypoxemia and DST Forward scores among those individuals without the risk allele (β=-0.03 (0.08), *P*=0.68). Additionally, the association between sleepiness scores and poorer DSC scores were twice as strong in individuals with the presence of APOE-ε4 genotype as opposed to those without, β=-2.40 (0.63), *P*<0.01, β=-0.91 (0.43), *P*<0.05, respectively. There were no interactions between AHI or SAS and APOE-ε4.

**Discussion**

Among an ethnically and socioeconomically diverse population of middle-age to older individuals, we found that sleep-related hypoxemia and daytime sleepiness were cross-sectionally associated with cognitive dysfunction, particularly tasks related to ~~processing speed,~~ attention and concentration, but not with a test of global cognitive function or working memory. The AHI was not associated with any cognitive tests in this study. Moreover, we found evidence that the associations between SDB and cognition varied by APOE-ε4. Specifically, we found that

APOE-ε4 carriers showed poorer attention and concentration as hypoxemia increased. Similarly, they showed poorer attention and slower processing speed as daytime sleepiness increased. Overall, these results suggest: a) overnight hypoxemia and self-reported sleepiness are more closely associated with cognitive function~~on~~ than the ~~, with little evidence that~~ AHI~~ is associated with cognitive function~~; b) associations with sleepiness persisted even after adjusting for sleep duration and sleep efficiency, suggesting that sleepiness may be a marker of SDB-related cognitive vulnerability; c) the most sensitive of our measures of cognitive impairment was the DST Forward, a measure of ~~short term memory~~attention and concentration; d) a genetic vulnerability to AD modified the key associations.

Prior studies have been inconsistent regarding the association between sleep-disordered breathing and cognitive function, perhaps due to population heterogeneity (with underlying differences in susceptibility to SDB-related changes in cognitive function), level of severity of SDB among samples studied, and differences in methods and measures employed, including the range of cognitive assessments administered and cognitive domains assessed. Our findings are generally consistent with prior research that has reported that the severity of hypoxemia was related to poorer cognitive performance.[13,14,20,22,34,44] Hypoxemia is thought to contribute to neurologic dysfunction through several pathways, including triggering of cellular events leading to apoptosis of hippocampal cells.[45] Cerebral vascular damage also may result from hypoxemia related chemoreflex activation, sympathetic vasoconstriction, and nocturnal blood pressure surges.[46,47] Intermittent hypoxemia influences both oxidative stress and inflammation, which can result in cognitive deficits by inducing neuronal cell loss within specific regions of the brain that lead to deficits.[48]

We also observed significant associations between daytime sleepiness and cognition, and showed that these associations persisted after adjusting for sleep duration and sleep efficiency.

These findings are consistent with the research of Cohen-Zion and colleagues, who found that increases in daytime sleepiness were associated with decreased cognitive performance.[17] Similarly, among two separate adult populations, excessive daytime sleepiness was also associated with increased risk of cognitive impairment; and the authors suggest that daytime sleepiness could be a marker for cognitive decline.[49,50] Reduced alertness resulting from sleepiness has been shown to decrease brain activity and function.[51] Although cognitive deficits may be directly due to sleepiness (and reduced vigilance), sleepiness also may provide an integrative measure of the effects of multiple sleep disrupting exposures that may contribute to cognitive decline, serving as a marker that identifies those most vulnerable to SDB.[52] Although sleepiness is not specific to SDB, our associations persisted after adjusting for both sleep duration and sleep efficiency, suggesting that insufficient sleep was not an explanation for our results. Results were slightly attenuated when adjusting for depressive symptoms, and underscore the possibility that altered mood also may be a marker or mediator of cognitive changes occurring with SDB. Sleep disturbance, fatigue and difficulty concentrating are cardinal features of depression.[53]

Notably, the AHI was not associated with none of the cognitive outcomes. Although the AHI is a standard clinical metric, there is increasing recognition that this measure has a number of limitations and does not provide specific information regarding physiological disturbances (e.g., may reflect different degrees of arousal and patterns of breathing and sleep disruptions). Recent studies of cognitive function in children also have shown no associations between the AHI and a comprehensive and sensitive cognitive battery, but showed associations between sleepiness, or Sleep Apnea Syndrome (defined by a mildly elevated AHI and elevated ESS score) and cognition.[54] Further, current definitions of AHI allow for significant variation in level of hypoxemia across patients, and a 3 or 4% decrease in oxygen desaturation can result in levels of oxyhemoglobin that are still well within normal ranges and not indicative of hypoxemia. Our results suggest the clinical assessment of sleepiness may be useful in identifying patients at increased risk for cognitive deficits associated with SDB.

The MESA cognitive battery was chosen to provide an broad assessment of cognitive performance across different several domains. We -found that our sleep measures were mostly related to tests of attention, concentration, and short-term memory, cognitive domains also observed to be impacted in other studies of patients with SDB.[13,15,19] Of all tests, the DST Forward was most consistently associated with sleepiness and hypoxemia. In contrast, a more cognitively challenging test, Digit Span Backwards, was not. One explanation for this seemingly counter intuitive finding is that tasks that are more demanding may result in greater cognitive activation, and help recruit compensatory mechanisms that overcome attentional deficits.[55] Neuroimaging studies provide evidence for such compensatory cognitive activation, particularly in the middle-age to older adulthood age-range,[56] and compensatory cerebral activation during cognitive processing has been documented in APOE-ε4 carriers.[57] Since DST Backward is more difficult than DST Forward, participants may have increased their effort in the conduct of DST Backward.

However, it is also important to note that DST Backward and DST Forward measure overlapping but different cognitive functions.[58] DST Backward is well documented to capture cognitive control and executive functioning processes, while DST Forward is considered to be a measure of attention and short-term memory that does not place high demands on executive processes such as sequencing and planning. While some studies have observed a negative impact of SDB on a broad range of executive function tasks, including both DST Forward and DST Backward,[59] similar to our own observation, others find a negative impact on DST Forward but not DST Backward suggesting SDB impacts attention and short-term memory.[60] Also, among e4 carriers, SDB is most consistently observed to negatively impact memory tasks.[28,61]

It is noteworthy that associations were not observed between sleep measures and a test of ~~global~~ overall cognitive measure of cognition, the CASI, which may lack sufficient sensitivity. Characteristics of our cohort, a middle-aged, male and female, and community sample may have attenuated the associations. It is also possible that residual confounding was present in associations with the CASI where cultural differences may be involved despite our adjustments in models. We did not observe an association of memory function and hypoxemia on the CASI, but the memory component only consists of recall of three words, which may not have been sufficiently sensitive to hypoxemia-associated memory impairment. Further, unlike older, clinic samples where patients are often concerned about cognitive function, our sample was not selective for either sleep related health or cognitive problems.

There is growing recognition that there is large population variability in susceptibility to various exposures, which has stimulated the emergence of "precision medicine." An important finding of our work is the observed effect modification by APOE-ε4. Notably, APOE-ε4 carriers had stronger associations between hypoxemia and attention/concentration as well as between sleepiness and processing speed. Our findings are consistent with several studies.[28,34,62,63] Data from the Wisconsin Sleep Cohort, showed an association between AHI and memory and executive function in carriers of the APOE-ε4 allele;~~,~~ however other measures of SDB were not assessed.[28] In a sample of older women, AHI, central apnea index, and oxygen saturation nadir less than 90% were associated with a higher risk of cognitive impairment among APOE-ε4 carriers.[34] In our diverse cohort, we found that those with the risk allele appeared more vulnerable to the influence of overnight hypoxemia and sleepiness on attention, memory and processing speed than those without a risk allele. These associations are plausible given that

SDB-related hypoxemia and oxidative stress most negatively impacts brain function in individuals genetically susceptible to synaptic degeneration.

It is noteworthy that other studies have observed lower performance on the Digit Span and DSC Tests to be predictive of cognitive decline and conversion to Mild Cognitive Impairment (MCI), as well as conversion from MCI to Alzheimer's Disease. Kurt and colleagues, found that lower digit span performance in older adults with subjective memory complaints predicted future neuropsychological test performance indicative of MCI.[64] In a larger cohort of 148 elderly adults with MCI, performance on the DSC was one of the strongest predictors of time to convert to Alzheimer's Disease.[65] MCI encompasses a range of cognitive deficits, some of which may present before others.[66] SDB-associated performance deficits in digit span measures of attention, speed of processing and working memory may be the first to capture subtle cognitive impairments that are indicative of subsequent MCI and dementia. While longitudinal studies are required to more fully investigate this possibility, the clinical implications are substantial. Along with APOE-ε4 risk -allele status, MCI status is one of the most robust risk factors for the development of dementia.

Given the current lack of effective treatments for AD and dementia there is a significant focus on secondary prevention, with recent research supporting the value in targeting multiple ~~identifying~~ modifiable risk factors.[67–69] ~~.~~Although each risk factor may individually have small effect, indices that include multiple behavioral, lifestyle and somatic risk factors together may account for as much as 50% of the excessive risk for dementia.[68,69] The association of SDB with dementia,[13,14] and poorer performance on cognitive function measures, suggest~~s~~ that SDB represents an additional modifiable risk factor to reduce the risk of conversion from typical aging to MCI, and from MCI to dementia. Although our average effect estimates for SDB indices were small, they were significant even after adjustment for traditional risk factors such as age, hypertension and diabetes.

This study contributes to the literature in several additional ways. We analyzed indices of SDB with three well-standardized neuropsychological tests. Standardized polysomnography allowed us to adjust for objective measures of sleep duration and sleep efficiency. Our study cohort was ethnically and racially diverse, providing greater generalizability than prior studies. Genetic data allowed us to test for effect modification. Despite these strengths, our study also has limitations. Although we included several sleep measures, these were derived from a single night of PSG, which does not capture variation over time. It is possible that duration of SDB and age of onset are important factors in influencing cognitive function. Our analyses were cross-sectional which does not allow us to infer causality. Lastly, it is possible that more sensitive cognitive tests would have yielded different results. Given the correlation among exposures and outcomes, we did not adjust for multiple comparisons.

*Conclusion*

Cognitive impairment is highly prevalent among elderly populations, and is associated with increased disability, neuropsychiatric symptoms and health care costs.[70–72] Our results suggest that more severe overnight hypoxemia and sleepiness may be related to poorer cognitive function, especially attention, concentration, and process speed in middle-aged to older adults, and that the risk is greater among carriers of the APOE-ε4 alleles, a known risk factor for Alzheimer's disease. With use of this type of information, future risk stratification may help to identify individuals at increased risk for SDB-related cognitive deficits and target those individuals for studies evaluating the impact of treatment or prevention.

**Table 1.** Study Population Characteristics by Sleep-Disordered Breathing (N=1752)

| Characteristic | Sleep-Disordered Breathing (AHI≥15) | | *P*-Value* |
|---|---|---|---|
| | Yes (n=585) Mean (SD) or No. (%) | No (n=1167) Mean (SD) or No. (%) | |
| Age, y | 68.6 (8.8) | 67.9 (9.2) | 0.11 |
| Male | 356 (60.8) | 440 (37.7) | <0.001 |
| Education | | | 0.05 |
| <HS | 94 (16.1) | 156 (13.4) | |
| HS or GED | 86 (14.7) | 203 (17.4) | |
| Some College | 156 (26.7) | 262 (22.5) | |
| ≥College | 249 (42.6) | 543 (46.6) | |
| Income | | | |
| <$25,000 | 175 (30.5) | 289 (25.4) | 0.16 |
| $25-$49,999 | 144 (25.1) | 309 (27.1) | |
| $50-$74,999 | 95 (16.6) | 205 (18.0) | |
| ≥$75,000 | 159 (27.7) | 336 (29.5) | |
| Race/Ethnicity | | | 0.10 |
| Non-Hispanic White | 197 (33.7) | 453 (38.8) | |
| Chinese | 79 (13.5) | 131 (11.2) | |
| African American | 152 (26.0) | 309 (26.5) | |
| Hispanic | 157 (26.8) | 274 (23.5) | |
| Body Mass Index | 30.5 (5.8) | 27.6 (5.1) | <0.001 |
| COPD | 11 (1.9) | 23 (2.0) | 0.90 |
| Depressive Symptoms | 8.0 (7.1) | 8.1 (7.8) | 0.83 |
| Antidepressant use | 3 (0.5) | 15 (1.3) | 0.13 |
| Benzodiazepine use | 14 (2.4) | 66 (5.6) | 0.002 |
| Current Smoker | 32 (5.5) | 87 (7.5) | 0.12 |
| Physical Activity, h per day | 9.0 (5.9) | 9.6 (6.1) | 0.05 |

| | | | |
|---|---|---|---|
| Total Sleep Time[a], min | 392.5 (75.3) | 387.7 (83.7) | 0.23 |
| Sleep Efficiency[a] | 89.9 (3.6) | 89.8 (3.8) | 0.65 |
| % REM[b] | 16.6 (6.9) | 19.1 (6.1) | <0.001 |
| % Slow Wave Sleep[b] | 8.4 (8.2) | 10.9 (9.2) | <0.001 |
| AHI, median (IQR) [b] | 32.2 (19.4-41.2) | 5.6 (2.0-9.0) | <0.001 |
| Arousal Index[b] | 29.5 (13.2) | 18.4 (8.9) | <0.001 |
| % Time Oxyhemoglobin Saturation <90%[b], median (IQR) | 8.2 (1.6-9.4) | 1.6 (0.0-0.97) | <0.001 |
| Sleep Apnea Syndrome | 97 (16.8) | 71 (6.2) | <0.001 |
| Epworth Sleepiness Scale | 6.4 (4.3) | 5.8 (3.9) | 0.01 |
| APOE-ε4 allele | 150 (26.7) | 297 (26.8) | |

IQR=Interquartile range; *chi-square or ANOVA tests for categorical or continuous variables (respectively); [a]Measures are based on actigraphy; [b]Measures are based on in-home polysomnography.

**Table 2.** Unadjusted Values (Mean, SD) of Cognitive Function Tests by Sleep-Disordered Breathing

| Cognitive Function | SDB | No SDB |
|---|---|---|
| CASI[c] | 87.6 (8.2) | 88.3 (8.4) |
| DSC[a] | 49.8 (18.2) | 53.0 (18.7) |
| Digit Span Forward | 9.5 (2.8) | 9.6 (2.8) |
| Digit Span Backward[c] | 5.5 (2.3) | 5.7 (2.4) |

CASI-Cognitive Abilities Screening Instrument (version 2); DSC-Digit Symbol Coding; [a]$P<0.01$, [b]$P<0.05$, [c]$P<0.10$

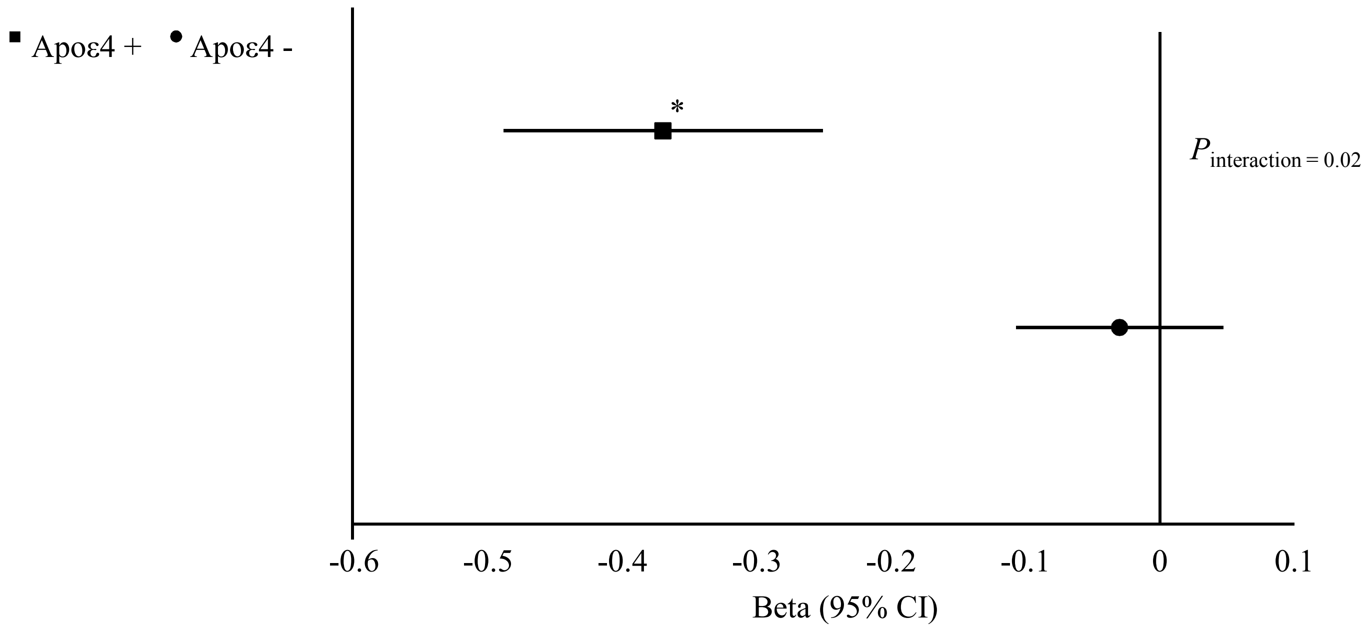
**Table 3.** Regression Analysis of Sleep-Disordered Breathing Indices and Cognitive Function, N=1752.

| | CASI | | | | DSC | | | | DST Forward | | | | DST Backward | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| AHI | 0.0004 (0.0023) | 0.0004 (0.0023) | 0.0005 (0.0023) | 0.0004 (0.0023) | -0.140 (0.354) | -0.016 (0.353) | -0.035 (0.354) | 0.089 (0.355) | 0.020 (0.064) | 0.032 (0.065) | 0.041 (0.066) | 0.064 (0.066) | -0.003 (0.053) | 0.017 (0.053) | 0.012 (0.054) | 0.015 (0.054) |
| % Saturation <90% | 0.004 (0.002)[c] | 0.004 (0.002)[c] | 0.004 (0.002)[c] | 0.004 (0.002)[c] | -0.693 (0.344) | -0.447 (0.341) | -0.428 (0.341) | -0.295 (0.341) | **-0.151 (0.063)[b]** | **-0.137 (0.063)[b]** | **-0.138 (0.063)[b]** | **-0.123 (0.063)[b]** | -0.027 (0.051) | -0.014 (0.052) | -0.011 (0.052) | -0.007 (0.052) |
| SAS | 0.001 (0.002) | 0.001 (0.002) | 0.001 (0.002) | ------ | **-0.903 (0.345)[a]** | **-0.698 (0.344)[b]** | **-0.694 (0.346)[b]** | ------ | -0.066 (0.062) | -0.056 (0.064) | -0.062 (0.064) | ----- | -0.011 (0.052) | -0.004 (0.052) | -0.002 (0.052) | ------ |
| ESS | 0.0005 (0.0022) | 0.0001 (0.0023) | 0.0003 (0.0023) | ------ | **-1.55 (0.345)[a]** | **-1.43 (0.344)[a]** | **-1.42 (0.346)[a]** | ------ | **-0.148 (0.063)[b]** | **-0.127 (0.064)[b]** | **-0.132 (0.064)[b]** | ----- | -0.035 (0.052) | -0.019 (0.052) | -0.014 (0.053) | ------ |

Model 1: Adjusted for age, sex, race, education level
Model 2: Model 1 + age, sex, race, education level, diabetes, hypertension, smoking
Model 3: Model 2 + sleep duration, sleep efficiency
Model 4: Model 3 + sleepiness
[a]*P*<0.01, [b]*P*<0.05, [c]*P*<0.10
Estimates are standardized
Shown are beta coefficients and standard errors

**Figure 1.**

**A.**




**B.**

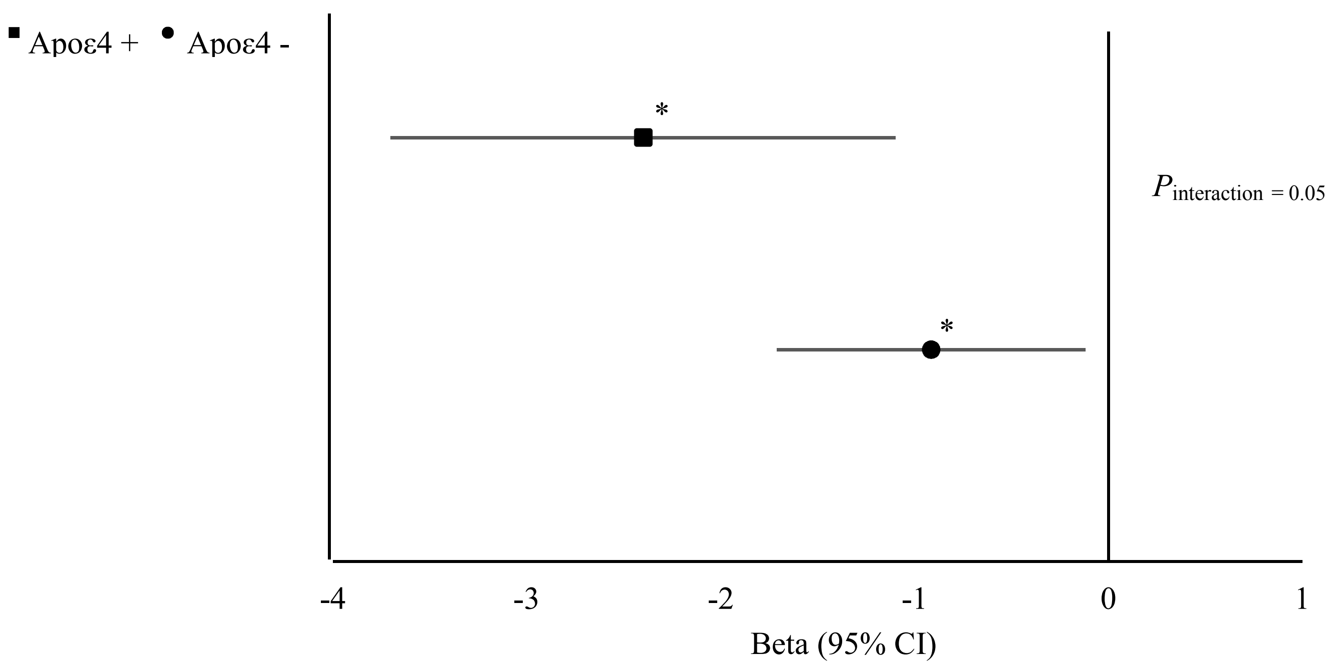



Figure 1illustrates forest plots showing the association between indices of SDB and cognitive tests by APOε4 risk allele. The data presented are the associations between sleep indices and cognitive outcome stratified by APOε4. (A) % Saturation <90% and Digit Span Forward Test by APOε4. (B) Epworth Sleepiness Scale and Digit Symbol Coding Test by APOε4.*$P$<0.05

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