Sleep-Disordered Breathing, Hypoxia, and Risk of Mild Cognitive Impairment and Dementia in Older Women

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Context  Sleep-disordered breathing (characterized by recurrent arousals from sleep and intermittent hypoxemia) is common among older adults. Cross-sectional studies have linked sleep-disordered breathing to poor cognition; however, it remains unclear whether sleep-disordered breathing precedes cognitive impairment in older adults. Objectives  To determine the prospective relationship between sleep-disordered breathing and cognitive impairment and to investigate potential mechanisms of this association. Design, Setting, and Participants  Prospective sleep and cognition study of 298 women without dementia (mean [SD] age: 82.3 [3.2] years) who had overnight polysomnography measured between January 2002 and April 2004 in a substudy of the Study of Osteoporotic Fractures. Sleep-disordered breathing was defined as an apnea-hypopnea index of 15 or more events per hour of sleep. Multivariate logistic regression was used to determine the independent association of sleep-disordered breathing with risk of mild cognitive impairment or dementia, adjusting for age, race, body mass index, education level, smoking status, presence of diabetes, presence of hypertension, medication use (antidepressants, benzodiazepines, or nonbenzodiazepine anxiolytics), and baseline cognitive scores. Measures of hypoxia, sleep fragmentation, and sleep duration were investigated as underlying mechanisms for this relationship.

Main Outcome Measures  Adjudicated cognitive status (normal, dementia, or mild cognitive impairment) based on data collected between November 2006 and September 2008.

Results  Compared with the 193 women without sleep-disordered breathing, the 105 women (35.2%) with sleep-disordered breathing were more likely to develop mild cognitive impairment or dementia (31.1% [n=60] vs 44.8% [n=47]; adjusted odds ratio [AOR], 1.85; 95% confidence interval [CI], 1.11-3.08). Elevated oxygen desaturation index (≥15 events/hour) and high percentage of sleep time (>7%) in apnea or hypopnea (both measures of disordered breathing) were associated with risk of developing mild cognitive impairment or dementia (AOR, 1.71 [95% CI, 1.04-2.83] and AOR, 2.04 [95% CI, 1.10-3.78], respectively). Measures of sleep fragmentation (arousal index and wake after sleep onset) or sleep duration (total sleep time) were not associated with risk of cognitive impairment.

Conclusion  Among older women, those with sleep-disordered breathing compared with those without sleep-disordered breathing had an increased risk of developing cognitive impairment.
Subsequent diagnoses of mild cognitive impairment and dementia to look for evidence that sleep-disordered breathing precedes cognitive impairment and assess possible mechanisms (hypoxia, sleep fragmentation, or sleep duration) to explain this association.

**METHODS**

**Study Population**

We studied participants enrolled in the Study of Osteoporotic Fractures, a multisite cohort study of community-dwelling women. Women who were aged 65 years or older and able to walk unassisted were recruited from population-based listings in 4 US areas: Baltimore County, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley, near Pittsburgh, Pennsylvania. A total of 9704 mostly white women were enrolled between September 1986 and October 1988 and 662 black women were enrolled between February 1997 and February 1998 (Figure). At each site, the institutional review boards approved the study and written informed consent was obtained from the participants.

At the eighth clinic visit (January 2002-April 2004), an ancillary study (Study of Osteoporotic Fractures’ Sleep and Cognition Study) was initiated at 2 of the clinical centers (Minneapolis and Pittsburgh; n = 2732). This eighth clinic visit of the Study of Osteoporotic Fractures is the baseline visit for the Sleep and Cognition Study. Eligible women were invited to participate in the polysomnography substudy. Potential participants were excluded if they reported use of a pressure mask (continuous positive airway pressure [CPAP] or bilevel positive airway pressure) or mouthpiece for snoring or sleep apnea during the past 3 months. In addition, participants were excluded if they had an open tracheostomy or reported regular use of oxygen therapy during sleep. Unattended overnight in-home polysomnography was completed in a convenience sample of 461 women.

Between November 2006 and September 2008 (ninth clinic visit; median follow-up: 4.7 [range, 3.2-6.2] years), 305 of the 461 participants with polysomnography completed a battery of neuropsychological tests and subsequently had their cognitive status determined between September 2008 and August 2009. Of the 156 women who did not attend the ninth clinic visit, 70 had died and 9 were previously terminated from the study. Seventy-seven women were excluded because they completed a minimal assessment visit (frequently collected by telephone). Of the 305 women who had a cognitive evaluation, 4 had missing or indeterminate cognitive data and were excluded and 3 women who screened positive for cognitive impairment (physician’s diagnosis of Alzheimer disease reported or low cognitive test score) also were excluded. Our analytic cohort comprised the 298 women with complete polysomnography data and cognitive assessment.

**Polysomnography**

Polysomnography data were collected in participants’ homes using the Compumedics Siesta Unit (Abbottsville, Australia). Channels included 2 central electroencephalograms, bilateral electrooculogram, chin electromyogram, thoracic and abdominal respiratory effort, airflow (using nasal-oral thermocouple and nasal pressure recording), finger pulse oximetry, electrocardiogram, body position, and bilateral piezoelectric sensors to detect leg movements. Data were evaluated by trained technicians and sleep stage was assessed in 30-second epochs according to standard criteria. Apneas (complete cessation of airflow) and hypopneas (discernible [>30%] reduction in airflow) were defined if occurring for 10 seconds or longer and accompanied by a 3% or greater oxygen desaturation. Arousals from sleep were defined as an abrupt shift in electroencephalogram frequency of 3 seconds or longer; arousals during rapid eye movement sleep required an increase in chin electromyogram activity.

Sleep-disordered breathing was measured by the apnea-hypopnea index.
(number of apnea plus hypopnea events per hour of sleep) and prevalent sleep-disordered breathing coded as an apnea-hypopnea index of 15 or more events per hour.12 Calculated variables used as indices of hypoxia included the oxygen desaturation index (defined as number of oxygen desaturations ≥3% per hour of sleep and coded as ≥15 or <15 events per hour); the percentage of sleep time with oxygen saturation (oxygen saturation <90% coded as ≥1% of sleep time or <1% sleep time with oxygen saturation <90%); and the percentage of sleep time in apnea or hypopnea (>3% of oxygen desaturation coded into tertiles). Calculated variables of sleep fragmentation included arousal index defined as number of arousals per hour of sleep and minutes of wake after sleep onset (both coded into tertiles). Sleep duration was measured as the total sleep time coded into tertiles.

Cognitive Assessment
The shortened Mini-Mental State Examination13 (a test of global cognition) and a modified version of Trails B14 (a test of executive function) were administered at all clinic visits including at baseline (ie, eighth clinic visit). At the follow-up visit (approximately 5 years later), an expanded neuropsychological test battery was administered to women participating in the Sleep and Cognition ancillary study. This battery included Trails B, the modified Mini-Mental State Examination13 (a 100-point extended version of the Mini-Mental State Examination that has superior accuracy for dementia screening16), the California Verbal Learning Test (second edition short form),17 Digit Span (from the Wechsler Adult Intelligence Scale–Revised),18 and category and verbal fluency tests.19

Cognitive impairment was determined in a 2-step process.20 First, women were screened for 1 or more of the following criteria: (1) score of less than 88 on the modified Mini-Mental State Examination; (2) score of less than 4 (delayed recall) on the California Verbal Learning Test; (3) score of 3.6 or greater on the Informant Questionnaire on Cognitive Decline in the Elderly21; (4) previous diagnosis of dementia or use of medication for dementia; or (5) nursing home residence. The women who screened positive had their clinical cognitive status adjudicated by a panel of clinical experts who were blinded to the women’s sleep-disordered breathing status. The panel reviewed all cognitive, self-reported medical history, and functional data. The women who screened negative were considered cognitively normal. A diagnosis of dementia was made based on Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria.22 Mild cognitive impairment was diagnosed using the modified criteria by Petersen et al23,24 (data on subjective memory loss was available for some but not all women), which requires cognitive impairment that is insufficient to meet criteria for dementia and reflects generally intact function.

Other Measures
Participants completed a questionnaire assessment of medical history and underwent a brief physical examination at each study visit. Information on age, race, height and weight, educational attainment, self-reported current smoking, self-reported history of a physician’s diagnosis of diabetes mellitus, hypertension, and stroke were included in the analyses as potential confounders. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. A score of 6 or greater on the Geriatric Depression Scale was used to define high depressive symptoms. Current use of medication was verified by examination of pill bottles; medications were categorized using a computerized coding dictionary according to brand or generic names.25 Drug categories included antidepressants, benzodiazepines, and non-benzodiazepine anxiolytics.

Statistical Analysis
We first determined median polysomnography parameters. To compare baseline characteristics of women with sleep-disordered breathing with those without sleep-disordered breathing, we used χ² and t tests. We then calculated unadjusted and multivariate logistic regression models to examine the association between sleep-disordered breathing and mild cognitive impairment or dementia. Multivariate models were adjusted for age, race, BMI, education level, smoking status, presence of diabetes, presence of hypertension, antidepressant use, benzodiazepine use, and use of nonbenzodiazepine anxiolytics; additional models were adjusted for cognitive test scores at baseline. Next, we examined models with individual measures of hypoxia and disordered breathing, sleep fragmentation, or sleep duration as predictors of cognitive impairment.

Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). A P value of less than .05 was considered significant and 2-sided tests were used. All statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS
Of the 298 women studied, most were white (n=269; 90.3%), had a mean age of 82.3 years, and 30.2% graduated from high school and attended college. Compared with the other women who attended the ninth clinic visit but did not participate in our study (n=1430), the 298 women who participated were younger, had slightly greater BMIs, and slightly better cognitive scores at the eighth clinic visit (mean age: 82.3 years vs 83.5 years, respectively, P <.001; mean BMI: 28.2 vs 27.1, P <.001; mean Mini-Mental State Examination score: 25.0 vs 24.5, P=.002; and mean Trails B score: 127.6 vs 159.2, P <.001), but did not differ on other characteristics. The median apnea-hypopnea index and oxygen desaturation index were 10.0 and 14.5 events per hour of sleep, respectively. Among the 298 women, 105 (35.2%) met criteria for sleep-disordered breathing with an apnea-hypopnea index of 15 or more events per hour. Women with and without
sleep-disordered breathing did not differ on baseline characteristics (Table 1). Median total sleep time was 6.0 hours; there was a median of 18.0 arousals per hour of sleep and a median wake after sleep onset of 79.0 minutes (Table 2).

After a mean of 4.7 years of follow-up, 107 (35.9%) women developed mild cognitive impairment or dementia (mild cognitive impairment: n = 60 [20.1%]; dementia: 47 [15.8%]). Women who developed mild cognitive impairment or dementia had lower baseline scores on cognitive tests but otherwise did not differ on baseline characteristics from those who did not develop cognitive impairment or dementia. Forty-seven women (44.8%) with prevalent sleep-disordered breathing developed mild cognitive impairment or dementia compared with 31.1% (60/193) of those without sleep-disordered breathing (P = .02).

The presence of sleep-disordered breathing was associated with an increased odds of subsequent mild cognitive impairment or dementia (OR, 1.80; 95% CI, 1.10-2.93). Adjustment for age, race, BMI, education level, smoking status, presence of diabetes, presence of hypertension, antidepressant use, benzodiazepine use, and use of nonbenzodiazepine anxiolytics led to similar results (OR, 1.85; 95% CI, 1.11-3.08). Additional adjustment for baseline cognitive test scores strengthened the association (OR, 2.36; 95% CI, 1.34-4.13). When mild cognitive impairment and dementia were analyzed separately, results were consistent with the combined analysis, although with reduced power to detect a difference (eTable at http://www.jama.com).

We also investigated the relationship of hypoxia, sleep fragmentation, and a measure of sleep duration on risk for mild cognitive impairment or dementia. Two measures of hypoxia (an oxygen desaturation index of ≥15 and a high percentage of total sleep time [≥7%] in apnea or hypopnea) were associated with higher incidence of mild cognitive impairment or dementia (oxygen desaturation index: OR, 1.67 [95% CI, 1.03-2.69]; sleep time in apnea or hypopnea: OR, 1.79 [95% CI, 1.01-3.20]; Table 3).

Sleep time with an oxygen saturation of less than 90% was not significantly associated with mild cognitive impairment or dementia. Conversely, no significant association was seen for the sleep fragmentation or sleep duration measures of arousal index, wake after sleep onset, or total sleep time before or after adjustment for covariates. Measures of hypoxia remained significant even after adjusting for covariates and baseline cognitive test scores (oxygen desaturation index: OR, 1.98 [95% CI, 1.15-3.43]; sleep time in apnea or hypopnea: OR, 2.32 [95% CI, 1.19-4.54]).

**COMMENT**

Among older women, sleep-disordered breathing was associated with an increased risk of developing cognitive impairment 5 years later. In addition, even after adjusting for demographic risk factors and comorbidities, we found that 2 of 3 indices of hypoxia but not sleep fragmentation or sleep duration were associated with incident mild cognitive impairment or dementia, suggesting that hypoxia is a likely mechanism through which sleep-disordered breathing increases risk for cognitive impairment.

Prior cross-sectional studies of sleep-disordered breathing and cognitive function in elderly populations have reported conflicting results; some inves-
tigations have reported associations of sleep-disordered breathing with either lower cognitive test scores or dementia, while others have not. Such divergent findings could be due to differences in the measurement and definition of sleep-disordered breathing or of cognitive impairment. These earlier cross-sectional studies are also limited in establishing the causal pathway of this association. Our investigation is the first, to our knowledge, to report on the longitudinal relationship between sleep-disordered breathing and risk of mild cognitive impairment or dementia.

We explored possible mechanisms (hypoxia and sleep fragmentation or duration) through which sleep-disordered breathing might increase the risk for cognitive impairment. Sleep itself plays a critical role in the consolidation of long-term memory, which occurs during slow-wave sleep. While experimental studies have reported inconsistent effects of sleep fragmentation and hypoxia on deficits in neurocognitive performance, the literature does not extend to the long-term effects of sleep on cognition.

In our study, none of the sleep fragmentation or duration measures had a significant association with cognitive impairment after accounting for potential confounders, while the hypoxia measures were consistently associated with mild cognitive impairment or dementia. This suggests that hypoxia is a likely mechanism for this relationship, which is supported by recent animal models of chronic hypoxia that demonstrated similar impairments in cognition with possible implications for apolipoprotein E, inflammatory, and regulatory pathways. However, it is important to note that because cerebral blood flow may be affected in elderly patients, other mechanisms such as hypercapnia could also be involved.

In patients with Alzheimer disease, therapeutic trials of treatment with CPAP for sleep-disordered breathing have been shown to slow or even improve cognitive impairment. Furthermore, a recent investigation of individuals with sleep apnea indicated that treatment with CPAP not only improved cognitive scores, but also increased gray matter volume in the hippocampal and frontal regions.

To fully evaluate the impact of treatment for sleep-disordered breathing in elderly populations, additional trials with larger sample sizes, longer treatment periods, and more diverse populations are required. Of interest, our findings suggest a potential role for supplemental oxygen therapy for sleep-disordered breathing in elderly individuals; however, its role requires critical evaluation in intervention studies. In addition, future studies should consider the association of sleep-disordered breathing with impairment in specific cognitive domains as well as changes in these variables over time.

Both the oxygen desaturation index and percentage time in apnea or hypopnea were associated with incident cognitive impairment. The oxygen desaturation index is a measurement of intermittent hypoxemia while the time in apnea or hypopnea estimates the proportion of the sleep period during which the respiration consists of apneas and hypopneas. Unlike the apnea-hypopnea index, which is simply a count of apneas plus hypopneas per hour of sleep (can be elevated when breathing disturbances occur frequently but are of brief duration), the percentage of time in apnea or hypopnea reflects both the frequency and duration of breathing disturbances and thus may better reflect sleep-related gas...
Percentage of time in oxyhemoglobin desaturation, as measured by sleep time with oxygen saturation of less than 90% in our study, is another measure of sleep-related hypoxemia and was not significantly associated with mild cognitive impairment or dementia; however, it may not reflect the effects of intermittent hypoxemia as well as the other 2 indices of hypoxemia. Studies suggest intermittent hypoxia, rather than continuous hypoxia, is associated with greater risk of oxidative stress and adverse outcomes. 39,40

Although our prospective design with objective measures of sleep-disordered breathing and rigorous methods to diagnose cognitive impairment supports the hypothesis that sleep-disordered breathing precedes dementia, there are several limitations that warrant consideration. While measurement of polysomnography data in a sleep laboratory over multiple nights is the criterion standard, several studies indicate that polysomnography measures in the home vs in the laboratory and measures taken during 1 night vs multiple nights are reliable, although misclassification bias is possible. 41-43 In this study, polysomnography data was collected in the home for only 1 night so variability in sleep disturbance measures over time may not have been captured. Because the Study of Osteoporotic Fractures cohort is composed of mostly white women, these findings may not be generalizable to men or more ethnically diverse populations. Finally, because women with more severe sleep-disordered breathing or cognitive impairment were less likely to survive to the eighth and ninth decades of life, there may be a survival bias in our results, but this would most likely result in an underestimate of the association.

CONCLUSIONS

We found that among women with a mean age of 82 years, sleep-disordered breathing was associated with an increased risk of cognitive impairment. Our results indicate that this relationship seems to be related primarily to measures of hypoxia. Given the high prevalence of both sleep-disordered breathing and cognitive impairment among older adults, the possibility of an association between the 2 conditions, even a modest one, has the potential for a large public health impact. Furthermore, the finding that hypoxia and not sleep fragmentation or duration seems to be associated with risk of mild cognitive impairment or dementia provides clues to the mechanisms through which sleep-disordered breathing might promote cognitive impairment. The increased risk for cognitive impairment associated with sleep-disordered breathing opens a new avenue for additional research on the risk for development of mild cognitive impairment or dementia and exploration of preventive strategies that target sleep quality including sleep-disordered breathing.

Author Contributions: Dr Yaffe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Yaffe, Redline, Spira, Ancoli-Israel, Stone.

Acquisition of data: Redline, Ensrud.

Analysis and interpretation of data: Yaffe, Laffan, Harrison, Redline, Ancoli-Israel, Stone.

Drafting of the manuscript: Yaffe, Laffan, Harrison, Redline.

Critical revision of the manuscript for important intellectual content: Laffan, Redline, Spira, Ensrud, Ancoli-Israel, Stone.

Statistical analysis: Laffan, Harrison, Ancoli-Israel, Stone.

Obtained funding: Yaffe, Redline, Ancoli-Israel, Spira, Ensrud.

Administrative, technical, or material support: Yaffe, Laffan, Redline.

Study supervision: Yaffe, Stone.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Yaffe reported that she is a consultant for Novartis Inc; serves on data and safety monitoring boards for Pfizer, Meridian, and the National Institute of Mental Health; is a board member for Beeson Scientific Advisory; has grants pending with the National Institutes of Health, the Alzheimer Association, the Department of Defense, and the American Health Assistance Foundation; and has received funding for expenses unrelated to the activities listed from the Alzheimer Association, the National Institutes of Health, Beeson Scientific, Japan Geriatrics Society, Wake Forest University, and the State of California Department of Human Services. Dr Laffan reported that she received salary support and was reimbursed for travel to professional society meetings from the National Institutes of Health. Dr Redline reported that her institution received a California Pacific Medical Center subcontract via a National Institutes of Health grant; she is a board member for the American Academy of Sleep Medicine; her institution has received an endowment for a professorship in sleep medicine from Dr Peter Farrell, CEO of RosMed Inc; and has multiple grants pending with the National Institutes of Health on sleep apnea. Dr Spira reported that he has received honoraria as a clinical editor for the International Journal of Sleep and Wellness—Primary Care, which receives pharmaceutical industry support. Dr Ancoli-Israel reported that she is a consultant for Johnson & Johnson, Merck, Purdue Pharma LP, sanofi-aventis, and Pfizer and has grants pending with the National Institutes of Health.

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REFERENCES


