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Authors

Blackwell, Terri
Yaffe, Kristine
Laffan, Alison
et al.

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Associations of Sleep Disordered Breathing, Nocturnal Hypoxemia and Subsequent Cognitive Decline in Older Community-Dwelling Men: The MrOS Sleep Study

Terri Blackwell, MA[a], **Kristine Yaffe, MD**[b], **Alison Laffan, PhD**[a], **Susan Redline, MD, MPH**[c], **Sonia Ancoli-Israel, PhD**[d], **Kristine E. Ensrud, MD, MPH**[e], **Yeonsu Song, PhD**[a], **Katie L. Stone, PhD**[a], and **for the Osteoporotic Fractures in Men (MrOS) Study Group**

[a]Research Institute, California Pacific Medical Center, San Francisco, CA

[b]Departments of Psychiatry, Neurology, and Epidemiology, University of California, San Francisco, San Francisco, CA and the San Francisco VA Medical Center

[c]Departments of Medicine, Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

[d]Departments of Psychiatry and Medicine, University of California, San Diego, La Jolla, CA

[e]Center for Chronic Disease Outcomes Research, Veterans Affairs Medical Center, Minneapolis, MN; Department of Medicine and Division of Epidemiology & Community Health, University of Minnesota, Minneapolis, MN

Abstract

OBJECTIVES—Sleep-disordered breathing (SDB) is a group of disorders common among older adults, characterized by breathing pauses during sleep often accompanied by hypoxemia. Few studies have examined if SDB is associated with cognitive decline.

DESIGN—A population-based longitudinal study.

SETTING—6 centers in the United States.

PARTICIPANTS—2,636 community-dwelling older men (age 76.0 ± 5.3 years) without mild cognitive impairment, followed 3.4 ± 0.5 years.

Corresponding Author: Terri Blackwell, MA, San Francisco Coordinating Center, 185 Berry Street, Lobby 5, Suite 5700, San Francisco, CA 94107, Phone: (415) 600-7412; Fax: (415) 514-8150, tblackwell@sfcc-cpmc.net. **Alternate Corresponding Author:** Katie L Stone, PhD, San Francisco Coordinating Center, 185 Berry Street, Lobby 5, Suite 5700, San Francisco, CA 94107, Phone: (415) 600-7422, Fax: (415) 514-8150, kstone@sfcc-cpmc.net.

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Author Contributions:
Terri L. Blackwell – analysis and interpretation of data, preparation of manuscript
Kristine Yaffe, MD – interpretation of data, critical review of manuscript
Alison Laffan, PhD– interpretation of data, critical review of manuscript
Susan Redline, MD, MPH- study concept and design, acquisition of data, interpretation of data, critical review of manuscript
Sonia Ancoli-Israel, PhD- study concept and design, interpretation of data, critical review of manuscript
Kristine E. Ensrud, MD, MPH - study concept and design, acquisition of data, interpretation of data, critical review of manuscript
Yeonsu Song, PhD– interpretation of data, critical review of manuscript
Katie L Stone, PhD- study concept and design, acquisition of data, interpretation of data, critical review of manuscript

MEASUREMENTS—SDB, measured by in-home polysomnography: nocturnal hypoxemia [≥1% of sleep time with oxygen saturation (SaO_2) <90% vs. <1%; oxygen desaturation index (ODI: number of oxygen desaturations ≥3% per hour sleep)]; apnea-hypopnea index (AHI, number of apneas and hypopneas at ≥3% desaturation per hour sleep). Cognitive decline, measured by the Modified Mini-Mental State examination (3MS) and Trails B test at baseline and 2 follow-up timepoints. Associations of predictors and cognitive decline were examined with linear mixed models adjusted for multiple confounders. Models were further adjusted by potential mediators (sleep duration, sleep fragmentation, resting SaO_2).

RESULTS—Nocturnal hypoxemia was related to greater decline on the 3MS. Men with ≥1% of sleep time with SaO_2<90% had an adjusted annualized decline of 0.43 points compared to 0.25 for men in the referent group (P = .003). For each 5-point increase in ODI there was an average annualized decline of 0.36 points (P = .01). Results were robust to further adjustment for potential mediators. The association between AHI and cognitive decline did not reach significance. No associations were seen with SDB and decline on the Trails B test.

CONCLUSION—Among older community-dwelling men, there was a modest association of nocturnal hypoxemia with global cognitive decline, suggesting the importance of overnight oxygenation to cognitive function.

Keywords

sleep-disordered breathing; nocturnal hypoxemia; cognitive decline

INTRODUCTION

Sleep-disordered breathing (SDB) is a group of disorders characterized by pauses or reduction in breathing during sleep, often associated with hypoxemia. SDB is common among the elderly, with 25% of community-dwelling older men effected by moderate to severe SDB.[1] Cognitive impairment can be defined as cognitive decline greater than is expected for one's age and education level.[2] At least 10% of people 65 years old or older will develop cognitive impairment, with the rate rising exponentially with advancing age.[3,4] With the rate of cognitive impairment increasing[5] and the high prevalence of SDB in the elderly, it is important to determine prospective associations with SDB and cognitive decline.

Cognitive impairment has been shown to be associated to SDB, but most studies have been cross-sectional in nature which prevents conclusions on the direction of associations.[6–11] Of the few studies examining the longitudinal association of SDB and cognitive decline, some have been based on self-reported[12,13] rather than objectively[14,15] measured SDB predictors. One study of elderly women did find an association of objectively measured SDB to the development of mild cognitive impairment (MCI) or dementia.[15]

To test the hypothesis that SDB and its associated nocturnal hypoxemia are associated with cognitive decline in older men, data from 2,636 cognitively intact men aged 67 years and older enrolled in the multicenter Outcomes of Sleep Disorders in Men (MrOS Sleep) Study were examined. Polysomnography (PSG) recordings were collected in this cohort and 2

measures of cognition were evaluated at this time and at two subsequent timepoints an average of 1.2 and 3.4 years after the PSG recording. The MrOS Sleep Study provides a unique opportunity to study SDB and cognitive decline in a large cohort of community-dwelling older men who are well-characterized for sleep exposures and potentially important covariates, allowing for examination of possible mechanisms [sleep duration, sleep fragmentation, history of chronic obstructive pulmonary disease (COPD)] that could explain this association.

METHODS

Participants

During the Osteoporotic Fractures in Men Study (MrOS) baseline examination from 2000 to 2002, 5,994 community-dwelling men 65 years or older were enrolled at six clinical centers in the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California.[16,17] (Figure 1) In order to participate, men needed to be able to walk without assistance and must not have had a bilateral hip replacement.

The MrOS Sleep Study, an ancillary study of the parent MrOS cohort, recruited 3,135 participants for a comprehensive sleep assessment. Men were screened for nightly use of mechanical devices during sleep including pressure mask for sleep apnea [continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP)], mouthpiece for snoring or sleep apnea, or oxygen therapy and were excluded if they could not forgo use of these devises during an overnight PSG recording. Of the 2,859 men who did not participate in this ancillary study, 349 died before the sleep visit, 39 had already terminated the study, 324 were not asked because recruitment goals had already been met, 150 were ineligible, and 1,997 refused. (Figure 1)

This analysis used data gathered at the Sleep Visit (2003 – 2005), Visit 2 (2005 – 2006) and Visit 3 (2007 – 2009). To be included in this analysis, men had to have cognitive data at the Sleep Visit and one or both of the follow-up timepoints, and had not been classified as having “probable MCI” at the Sleep Visit (Modified Mini-Mental State examination (3MS) score <80 or on a medication for dementia).

Among the 3,135 participants of the MrOS Sleep Study, cognitive function data for either the Trail Making Test – Part B (Trails B) or the 3MS was available for 3,130 men. Of these, 2,908 men also had PSG data. One hundred forty-eight of these men were not included as they had probable MCI.

No exclusion criteria were used at Visit 2 and Visit 3. At both visits, the majority of men completed the clinic visit and had data collected on cognitive function. Of the 2,760 cognitively intact men with Sleep Visit PSG data, 2,636 provided data on cognition at either Visit 2 or Visit 3 (Visit 2: 2,580, 95% of survivors; Visit 3: 2,343, 92% of survivors) and comprise our analytic cohort.

All men provided written informed consent, and the study was approved by the Institutional Review Board at each site.

Polysomnography Measures

In-home sleep studies were completed using unattended, portable polysomnography (Safiro, Compumedics, Inc.®, Melbourne, Australia). The PSG recordings were to be gathered within one month of the clinic visit (mean 6.9 ± 15.8 days from visit), with 78% of recordings gathered within one week of the clinic visit. The recording montage was as follows: C_3/A_2 and C_4/A_1 electroencephalograms, bilateral electrooculograms and a bipolar submental electromyogram to determine sleep stage; thoracic and abdominal respiratory inductance plethysmography to determine respiratory effort; airflow (by nasal-oral thermocouple and nasal pressure cannula); finger pulse oximetry for measuring oxygen saturation; lead I EKG; body position (mercury switch sensor); and bilateral tibialis leg movements (piezoelectric sensors). Centrally-trained and certified staff performed home visits to set up the unit, verify the values of the impedances for each channel, confirm calibration of position sensors and note any problems encountered during set-up, similar to the protocol used in the Sleep Heart Health Study.[18] Staff returned the next morning to collect the equipment and download the data to the Central Sleep Reading Center (Cleveland, OH) to be scored by certified research polysomnologists. PSG data quality was excellent, with a failure rate of less than 4% and more than 70% of studies graded as being of excellent or outstanding quality.

Apnea was defined as complete or near complete cessation of airflow for >10 seconds, and hypopneas were scored if clear reductions in breathing amplitude (at least 30% below baseline breathing) occurred, and lasted >10 seconds.[19] In these analyses, only apneas and hypopneas that were each associated with a 3% or greater desaturation were included. This desaturation level complies with the alternate definition from the American Academy of Sleep Medicine for apneas and hypopneas and is comparable to the definition used in a previously published study.[15,20]

Indices of SDB examined include the apnea-hypopnea index (AHI), the oxygen desaturation index (ODI), the percent of time during overnight sleep in which arterial oxygen saturation was below 90% (% of sleep time with SaO_2 <90%), and the percent of time during overnight sleep spent in apnea or hypopnea. AHI was defined as the total number of apneas and hypopneas per hour of sleep. The inter-scorer reliability for AHI was high (ICC = 0.99). ODI was defined as the number of oxygen desaturations ≥3% per hour sleep.

The participants received a letter with the results of their PSG, primarily the value for the AHI. In addition, there were levels of apneic activity or hypoxemia considered so high that the likelihood of health risks or functional impairment may be substantial. The MrOS Sleep study elected an AHI level of ≥50 and a level of hypoxemic stress, defined as the time in desaturation (<75% SaO_2 level) for >10% sleep time, as levels that merited review by a local study physician (within 10 days of the PSG recording), with tailoring of specific feedback to participants and (if requested by participant) to physicians caring for these participants. The cutpoints used were approved by both the MrOS Steering Committee and the MrOS Sleep Observational Study Monitoring Board. The number of men with AHI ≥50

in this analysis subset was 95 (3.6%). Of those 95 men with AHI ≥50, 39 (41%) began treatment with CPAP sometime during the follow-up period for this analysis. No men met the criteria for hypoxemic stress.

Sleep duration and wake after sleep onset (WASO) were also measured by PSG.[21] WASO, a measure of sleep fragmentation, was defined as the minutes scored awake during the sleep period after sleep onset. Resting SaO_2 level was determined just prior to sleep after the set up of the unit using the PSG recorder's oximeter finger pulse.

Cognitive Assessment

Two tests of cognitive function were administered at the clinic visits by trained staff: the Trail Making Test – Part B (Trails B) and the Modified Mini-Mental State examination (3MS).

The Trails B is a timed test of processing speed that measures attention, sequencing, visual scanning and executive function. Executive function is a measure of the ability for planning or decision making, error correction or trouble shooting, and abstract thinking. The Trails B test requires the participant to continuously scan a page to identify numbers and letters in a specified sequence while shifting from number to letter sets.[22] The participant is given 300 seconds to complete the test. A lower time for completion (in seconds) represents better executive functioning. A positive increase in completion time represents cognitive decline (took longer to complete the test at the follow-up timepoint).

The 3MS is a global measurement of cognitive function, with components for orientation, concentration, language, praxis, and immediate and delayed memory. The 3MS test is a broad sampling of cognitive domains. Scores range from 0 to 100, with higher scores representing better cognitive functioning.[23] A decrease in 3MS score represents cognitive decline (score was lower at the follow-up timepoint).

Development of clinically significant cognitive decline from the Sleep Visit to Visit 3 (a mean of 3.4 ± 0.5 years later) was defined separately for each test as follows: having a decline of 5 points on the 3MS,[24] or being in the highest 10% of change score for Trails B (Visit 3-Sleep Visit change score ≥65 seconds).[25] Defining cognitive decline on the Trails B as the worst decile of change in completion time is an approach that has been used in a number of previous studies.[26–28]

Other Measures

All participants completed questionnaires at the time of the Sleep clinic Visit, which included items about demographics, medical history, self-reported health status, physical activity, smoking, caffeine intake and alcohol use. The number of prior medical conditions was calculated as the summed total of self-reported prior diagnoses of common chronic illnesses [hypertension, stroke or transient ischemic attack (TIA), diabetes, Parkinson's disease, COPD, coronary heart disease (CHD)]. The chronic illness of depression was assessed using the number of depressive symptoms from the Geriatric Depression Scale (GDS), with higher scores corresponding to higher levels of depression.[29] Participants were asked to bring in all current medications used within the preceding 30 days. All prescription

and nonprescription medications were entered into an electronic database and each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).[30] The use of antidepressants, benzodiazepines, and sleep medications (non-benzodiazepine, non-barbiturate sedative hypnotics) were categorized. Level of physical activity was assessed using the Physical Activity Scale for the Elderly (PASE).[31] Functional status was assessed by collecting information on five instrumental activities of daily living (IADL), which included walking two to three blocks on level ground, climbing up to ten steps, preparing meals, doing heavy housework, and shopping for groceries or clothing.[32,33] Self-reported caffeine intake was calculated based on answers to questions regarding intake of caffeinated coffee, tea and soda.[34]

A comprehensive examination included measurements of body weight and height. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Participants were asked about treatment for SDB as part of a postcard contact every four months. Response rate to these postcards exceeded 99%. One hundred seventy three men reported starting CPAP or oxygen therapy during sleep between the Sleep Visit and Visit 3, and 24 reported use at the Sleep Visit.

Statistical Analysis

The SDB parameters were expressed as categorical variables which were defined similarly to previous publications for comparability (AHI and ODI: <15, ≥15; percent of sleep time with SaO_2 <90%: <1%, ≥1%; percent of sleep time in apnea or hypopnea as quartiles).[15] Analyses were also performed to evaluate the linear relationship of the SDB parameters and cognition, with the SDB parameters expressed as continuous variables.

Summaries of the SDB parameters were summarized by median (interquartile range) due to the skewness of the parameters. Characteristics of participants were compared by category of ODI and AHI using chi-square tests for categorical variables, *t*-tests for normally distributed continuous variables, and Wilcoxon rank sum tests for continuous variables with skewed distributions. Similar comparisons were performed across categories of the other SDB parameters (data not shown).

Random-effects models were used to study the association between SDB parameters and changes in cognition over time. These models account for between-participant variation and within-participant correlation of repeated outcomes.[35] The random effect terms included both the intercept and the slope of the cognitive measurements over time, allowing for individual time trends for each participant. Variances and covariances were estimated using the restricted maximum likelihood method. Time was modeled as a continuous covariate, measured as years from the Sleep Visit. A quadratic term for time was considered to account for a nonlinear time trend; in all models the interaction of the quadratic term for time and the predictors were not significant so time was modeled linearly. Covariates (fixed effects) were selected for inclusion in a multivariable model by examining both the univariate association of the covariate and the SDB parameters and the association to the changes in the 3MS and

Trails B outcomes in unadjusted random-effects models. Age, race, clinic site, BMI and those covariates associated to both a SDB parameter and an outcome at $P < .10$ were kept in all multivariable models, which included education, number of depressive symptoms, history of diabetes, history of stroke or TIA, history of hypertension, history of CHD, history of Parkinson's disease, presence of an IADL impairment, benzodiazepine use, antidepressant use, self-reported health status, physical activity, alcohol use and smoking status. All continuous covariates were centered (value-mean) for use in the models. Change in cognition is presented as average change per year, calculated using the coefficients derived from the random-effects models. The continuous cognitive scores were transformed to meet model requirements (log transformation for Trails B, cube transformation for 3MS) and back-transformed for display of results.

The association of the SDB parameters with clinically significant cognitive decline was assessed using logistic regression models. Multivariable adjusted models were performed as described above. Results are presented as odds ratios and 95% confidence intervals (OR, 95% CI).

A number of secondary analyses were performed. Due to potential confounding, those 197 men who reported using CPAP or oxygen therapy during sleep at the beginning of the study or during follow-up were excluded from analyses. Multivariable models were further adjusted to include predictors of sleep duration and sleep fragmentation to determine if the associations of SDB parameters to cognitive decline were independent of these factors, which have been shown to be related cross-sectionally to cognition in this cohort.[36] Mulitivariable models were also further adjusted by resting SaO_2 level and history of COPD to determine if associations were mediated by these factors.

The SDB parameters of AHI, ODI and the percent of sleep time with SaO_2 <90% were as also categorized as quartiles in analyses. Results were similar (data not shown).

Lastly, although all analyses were pre-specified, a Bonferroni correction was applied to all significant *P*-values in the primary analysis to examine if the associations observed held after correction for multiple comparisons.

All significance levels reported were two-sided and all analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Participant Characteristics

The analysis cohort was comprised of 2,636 primarily Caucasian (90.5%) men with an average age of 76.0 ± 5.3 years at the first assessment. The men on average had high levels of global cognition at the initial visit (93.6 ± 4.5 points on the 3MS), and on average were similar to published norms for the Trails B completion time for community dwelling adults of similar age and education level (116.6 ± 49.9 seconds).[37] Of the 2,636 men studied, 43% had AHI ≥15, with a median AHI of 12.4 and a median ODI of 16 (Table 1). The median total sleep time was 6 hours, with a median of 101 minutes of WASO.

Many covariates differed significantly across categories of ODI (Table 2). Compared to men with ODI <15, those men with ODI ≥15 on average were older, had higher BMI, had more depressive symptoms, had lower levels of resting SaO_2 , less sleep and more sleep fragmentation. Men with ODI ≥15 were also more likely to have an IADL impairment or have had a history of hypertension, diabetes or CHD. They had lower levels of education, were less likely to report good or excellent health status, and had lower rates of benzodiazepine use than those men in the lower group. Compared to those men with <1% of their sleep time with SaO_2 <90%, those men with 1% or more of their sleep time spent with SaO_2 <90% were more likely to have a history of COPD and to have smoked in the past. Covariates associated to level of AHI were largely similar to those associated to category of ODI. AHI was not associated to presence of IADL impairment, history of CHD, self-reported health status or total sleep time. History of COPD and smoking status did not differ by category of AHI, ODI or quartile of the percent of sleep time in apnea or hypopnea.

Association of SDB and Cognitive Decline

By Visit 3, 3.4 ± 0.5 years later, on average the men declined on both cognitive tests. The unadjusted average increase in time to complete the Trails B test was 9.0 ± 49.0 seconds and the 3MS score was lower by 1.2 ± 5.5 points. Of clinical significance, at Visit 3 18.6% of men were considered to have cognitive decline based on the 3MS (5 point decline). Cognitive decline based on the Trails B test time was defined as the worst 10% in change scores, which was equivalent to an increase in test time of 65 seconds or more in this population.

There were no significant associations with any of the SDB parameters examined (AHI, ODI, % of sleep time with SaO2 <90%, % of sleep time in apnea or hypopnea) and change in Trails B test time (Table 3, Table 4). There was however a significant multivariable adjusted association seen with decline in 3MS score and 2 measures of nocturnal hypoxemia, ODI and the % of sleep time with SaO_2 <90%. Compared to those men with <1% of their sleep time with SaO_2 <90%, those men with 1% or more of their sleep time spent with SaO_2 <90% had over 1.5 times the annualized decline in 3MS score. Higher levels of ODI were associated with an accelerated decline in 3MS score (−0.36 decline per year for each 5 unit increase in ODI). Similar associations were observed between percent of sleep time spent in apnea or hypopnea and decline in 3MS score (−0.34 decline per year for each SD increase) but results did not meet statistical significance (P = .08).

Removing the 197 men who used CPAP or oxygen supplementation during sleep at the start of or during follow-up yielded similar results. The association of nocturnal hypoxemia and decline in 3MS score remained significant after further adjustment for sleep fragmentation (WASO) and sleep duration (P ≤.01). Results were unchanged after further adjustment for resting SaO_2 level or history of COPD.

No associations were observed between the SDB parameters and clinically significant cognitive decline (P >.17, Table 4).

In Tables 3 and 4 we performed 8 models per cognitive test, a total of 16 models per test. Adjusting the significance level of 0.05 with a Bonferroni correction would lead to a

significance cutpoint of P < 0.003125 (= 0.05/16). After applying this more stringent cutpoint for significance, the associations of hypoxemia to decline on the 3MS were no longer significant (p=0.01 for the association of ODI per 5-unit increase, p=0.03539 for ≥1% of sleep time with SaO_2<90% vs. <1%).

DISCUSSION

In this cohort of community-dwelling older men, there were modest associations of 2 indices of SDB-related nocturnal hypoxemia, ODI and the % of sleep time with SaO_2 <90%, with subsequent decline in global cognitive function, as measured by a decrease in 3MS score. The association of nocturnal hypoxemia to decline in the 3MS score was robust to further adjustment for sleep fragmentation, sleep duration, history of COPD and resting SaO_2 level. There were no associations seen with SDB and decline in executive function, measured by the Trails B test, nor with AHI and the decline of 3MS score.

In a prior cross-sectional study in the MrOS Sleep cohort, there was no association seen between nocturnal hypoxemia and the 3MS score, emphasizing the importance of examination of longitudinal change in cognition as well as cross-sectional associations.[6]

A prior analysis in the Study of Osteoporotic Fractures (SOF) examined the association of objectively measured SDB and cognitive decline in elderly women, and did find an association of objectively measured SDB and nocturnal hypoxemia to the development of MCI or dementia.[15] The SOF cohort was on average 6 year older, had 1.5 more years of follow-up, had lower levels of SDB and had lower levels of baseline cognitive functioning on average than the MrOS cohort in this current analysis. Two other studies examining the self-report of snoring and cognitive decline found conflicting results.[12,13] The assessment of snoring by self-report may be problematic because the participant may not be aware of their snoring behavior.[38] Snoring can be a poor predictor of SDB and does not identify severity of nocturnal hypoxemia.[39] A study examining the association of self-reported sleep apnea and incident dementia assessed over ten years of follow-up found an association with vascular but not nonvascular MCI or dementia.[12]

Data from animal studies support the association of recurrent intermittent hypoxemia and neuronal cell loss, which occurs in part due to increased inflammation and oxidative stress in neural tissue.[40,41] Animal studies have shown associations of intermittent hypoxemia with learning and memory deficits.[42,43] In a small study of young volunteers, acute intermittent hypoxemia exposure was related to decreases in working memory.[44] Patients with COPD, who have low levels of oxygen saturation, have been shown to have an increased rate of cognitive decline compared to those without COPD,[45–47] and among COPD patients resting hypoxemia was a strong predictor of incident cognitive impairment.[47] The findings of this study along with results from animal models and COPD studies suggest that nocturnal hypoxemia is likely a mechanism for cognitive decline. This may in part be due to the associations of oxidative stress, impaired glucose control, and inflammation to both hypoxemia and cognitive decline.[48,49]

The relationship observed with objectively measured nocturnal hypoxemia and decline on the 3MS and no associations with decline on the Trails B test may be because associations vary across specific domains of cognitive function. The association of SDB and cognitive decline is understudied. A study examining the cross-sectional relationship of objectively measured SDB with global cognition (Mini Mental State Exam, MMSE) and executive function (Trails B) found that nocturnal hypoxemia was related to MMSE but not to Trails B.[7]

The apnea-hypopnea index was not related to cognitive decline in this study. The AHI counts apneas and hypopneas per hour of sleep, which may be capturing when breathing is disturbed for short periods of time. The oxygen desaturation index is a measure of intermittent hypoxemia and the percent of time spent with SaO_2<90% reflect severity of hypoxemia. While these 2 measures are correlated (rho =0.61) they do reflect different aspects of hypoxemia.

This study has several strengths. The study had a large population of community-dwelling older men who were cognitively intact at the baseline timepoint. These men were not selected for inclusion based on sleep problems. Adjustments for multiple potential confounding factors were made, suggesting these associations were not explained by other covariates including depression, comorbidities, medication use, education, or lifestyle. Results were also robust to adjustment for sleep duration, sleep fragmentation and history of COPD.

This study also had several limitations. The findings may not be generalizable to population groups other than community-dwelling older men. Adjustment for numerous covariates was performed, but the possibility of residual confounding remains. We performed multiple comparisons, and some of our findings may be due to chance. Only a single night of polysomnography data was available, however, night-to-night reliability for AHI determined using home polysomnography is high.[50] An additional limitation is that our cognitive battery was limited and only included measures of global cognition and executive function. The Trail Making A test was not administered in this study. Thus we are unable to determine the time cost for executive control using the Trials B test time, independent of motor and visual control and speed. Finally, the absolute difference in cognitive decline between men with and without nocturnal hypoxemia was modest in magnitude and of uncertain clinical relevance.

In conclusion, among older community-dwelling men nocturnal hypoxemia associated with SDB, but not AHI, was related to greater subsequent cognitive decline. These associations were seen for global cognition and were modest in magnitude, but not observed for executive function. Further study is needed to examine if these associations hold after longer follow-up and vary by specific cognitive domains. More studies with adjudication of events such as development of MCI or dementia and categorization of these events as vascular or nonvascular would be beneficial. Exploration of possible underlying mechanisms of this potential association is also needed.

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Dr. Ancoli-Israel is a consultant or on the advisory board for Astra Zeneca, Ferring Pharmaceuticals Inc, GaxoSmithKline, Hypnocore, Johnson & Johnson, Merck, NeuroVigil Inc, and Purdue Pharma LP.

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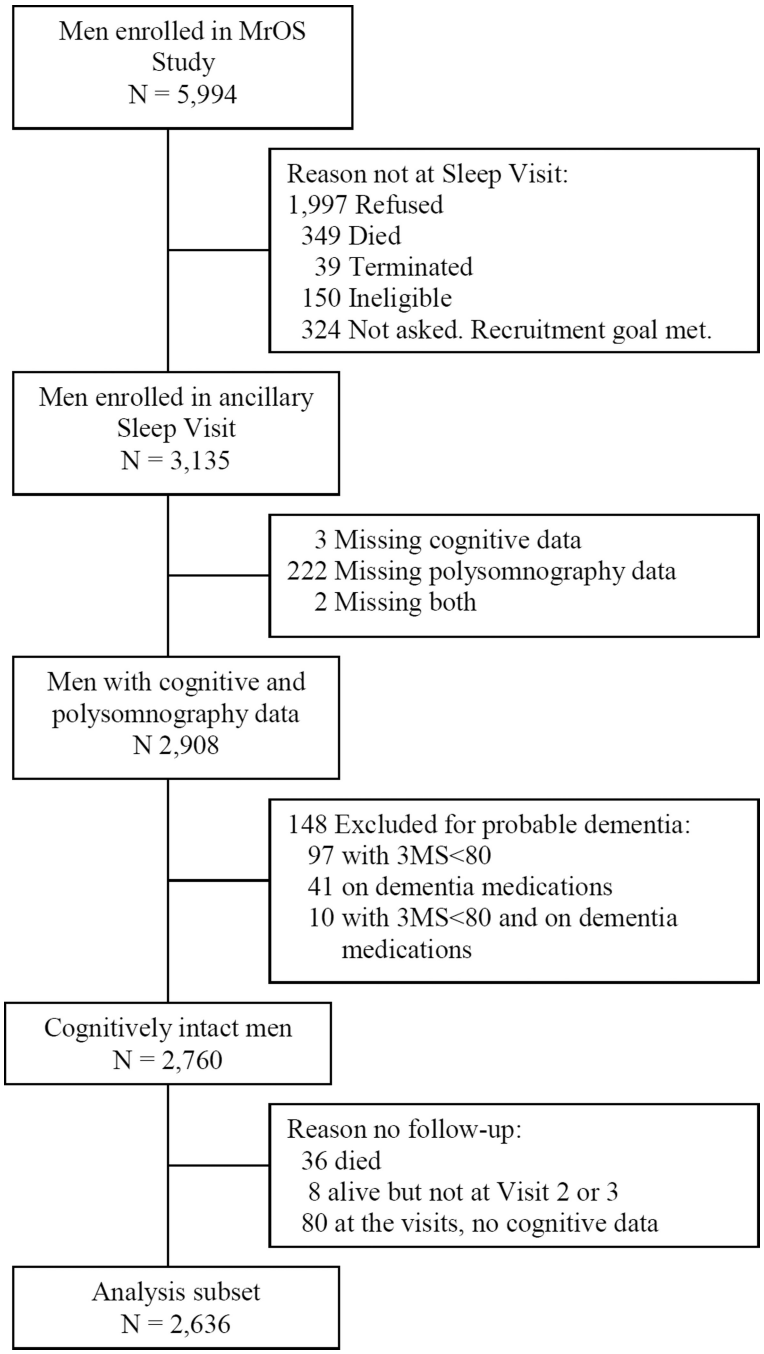

Figure 1.
Progression of Participants through the MrOS and MrOS Sleep Studies

Table 1

Sleep-Disordered Breathing Measures (n = 2,636)

Characteristic	Median (IQR)
Apnea-hypopnea index, events/h of sleep	12.4 (5.9 – 23.5)
Oxygen desaturation index, events/h of sleep	16.0 (8.9 – 28.5)
Sleep time with SaO_2<90%, %	1.0 (0 – 3.2)
Sleep time in apnea or hypopnea with ≥3% desaturation, %	9.7 (4.6 – 18.4)

Abbreviations: IQR, interquartile range; SaO_2, oxygen saturation.

Table 2

Baseline Characteristics by Oxygen Desaturation Index and Apnea-Hypopnea Index (n = 2,636)

	ODI		AHI	
Characteristic	**<15 (n = 1,219)**	**≥15 (n = 1,417)**	**<15 (n = 1,504)**	**≥15 (n = 1,132)**
Age, mean ± SD, y	75.8 ± 5.4	76.3 ± 5.3[b]	75.8 ± 5.3	76.4 ± 5.2[c]
Body mass index, mean ± SD, kg/m^2	26.2 ± 3.3	28.1 ± 3.9[d]	26.5 ± 3.5	28.1 ± 3.9[d]
Race/Ethnicity, n (%)				
Caucasian	1,113 (91.3)	1,300 (91.7)	1,380 (91.8)	1,033 (91.3)
African American	30 (2.5)	45 (3.2)	43 (2.9)	32 (2.8)
Other	76 (6.2)	72 (5.1)	81 (5.4)	67 (5.9)
One or more IADL impairments, n (%)	206 (16.9)	304 (21.5)[c]	273 (18.2)	237 (20.9)
History of selected medical conditions, n (%)				
Hypertension	551 (45.2)	748 (52.8)[d]	685 (45.6)	614 (54.2)[d]
Stroke or transient ischemic attack	115 (9.4)	161 (11.4)	152 (10.1)	124 (11.0)
Diabetes mellitus	126 (10.3)	214 (15.1)[d]	168 (11.2)	172 (15.2)[c]
Parkinson's disease	14 (1.2)	15 (1.0)	20 (1.3)	9 (0.8)
Chronic obstructive pulmonary disease	55 (4.5)	77 (5.4)	78 (5.2)	54 (4.8)
Coronary heart disease[a]	368 (30.2)	480 (34.0)[b]	461 (30.7)	387 (34.3)
Current antidepressant use, n (%)	73 (6.0)	108 (7.6)	101 (6.7)	80 (7.1)
Current benzodiazepine use, n (%)	64 (5.3)	49 (3.5)[b]	79 (5.3)	34 (3.0)[c]
Current non-benzodiazepine anxiolytic/hypnotic use, (n (%)	28 (2.3)	29 (2.1)	35 (2.3)	22 (1.9)
Geriatric Depression Scale score (range 0 to 15), mean ± SD	1.5 ± 2.0	1.8 ± 2.1[d]	1.6 ± 2.0	1.8 ± 2.1[d]
Depression, Geriatric Depression Scale score ≥6, n (%)	57 (4.7)	85 (6.0)	76 (5.1)	66 (5.8)
Education, n (%)				
< high school	43 (3.5)	77 (5.4)[d]	57 (3.8)	63 (5.6)[d]
high school	140 (11.5)	271 (19.1)	187 (12.4)	224 (19.8)
>high school	1,036 (85.0)	1,069 (75.4)	1,260 (83.8)	845 (74.7)
Alcohol intake, drinks/week, n (%)				
0–2	539 (44.5)	658 (46.6)	680 (45.5)	517 (45.9)
3–13	611 (50.5)	668 (47.3)	735 (49.1)	544 (48.3)
≥14	61 (5.0)	86 (6.1)	81 (5.4)	66 (5.9)
Smoking, n (%)				
Never	486 (39.9)	567 (40.0)	591 (39.3)	462 (40.8)
Past	701 (57.5)	827 (58.4)	876 (58.2)	652 (57.6)
Current	32 (2.6)	23 (1.6)	37 (2.5)	18 (1.6)
Caffeine use, mean ± SD, mg/day	243.5 ± 262.1	232.9 ± 231.3	244.5 ± 256.4	228.9 ± 231.4
PASE physical activity score, mean ± SD	149.1 ± 69.0	147.3 ± 72.2	149.0 ± 70.7	146.9 ± 70.8
Self-rated health good/excellent, n (%)	1092 (89.7)	1214 (85.7)[c]	1331 (88.6)	975 (86.1)
Resting SaO_2 level, mean ± SD, %	95.4 ± 1.6	94.8 ± 1.7[d]	95.3 ± 1.6	94.8 ± 1.7[d]

	ODI		AHI	
Characteristic	**<15 (n = 1,219)**	**≥15 (n = 1,417)**	**<15 (n = 1,504)**	**≥15 (n = 1,132)**
Sleep duration, mean ± SD, hr	6.0 ± 1.1	5.9 ± 1.2[c]	6.0 ± 1.1	5.9 ± 1.1
Wake after sleep onset, mean ± SD, min	103.9 ± 60.9	120.8 ± 67.4[d]	105.7 ± 62.5	122.6 ± 67.1[d]

Abbbreviations: ODI, oxygen desaturation ides. AHI, apnea-hypopnea index. SD, standard deviation. SaO_2, oxygen saturation. IADL, instrumental activities of daily living. PASE, Physical Activity Scale for the Elderly.

P-values for continuous data are from a *t*-test for normally distributed data, Wilcoxon rank sum test for skewed data. *P*-values for categorical data are from a chi-square test.

[a] Coronary heart disease includes a history of myocardial infarction, angina, congestive heart failure, bypass surgery, angioplasty or pacemaker placement.

[b] *P*-value <0.05;

[c] *P*-value <0.01;

[d] *P*-value <0.001.

Table 3

Adjusted[a] Annualized Mean Cognitive Decline by Sleep Disordered Breathing Parameter

	Trails B (sec)		3MS Score	
Predictor	**Change per year**	***P*-value**	**Change per year**	***P*-value**
Apnea-hypopnea index, events/h				
<15 (n = 1,504, reference)	2.09	Ref	−0.30	Ref
≥15 (n = 1,132)	2.03	.91	−0.39	.16
Continuous, per 5-unit increase	2.03	.67	−0.35	.18
Oxygen desaturation index, events/h				
<15 (n = 1,219, reference)	2.07	Ref	−0.29	Ref
≥15 (n = 1,417)	2.01	.93	−0.38	.17
Continuous, per 5-unit increase	2.17	.31	−0.36	.01
Sleep time with SaO_2 <90%, %				
<1 (n = 1,284, reference)	1.92	Ref	−0.25	Ref
≥1 (n = 1,352)	2.22	.59	−0.43	.004
Continuous, per SD increase (9.45)	2.27	.53	−0.40	.07
Sleep time in apnea or hypopnea, %				
Quartile 1: <4.6 (n = 659, reference)	2.11	Ref	−0.40	Ref
Quartile 2: 4.6 to <9.7 (n = 659)	2.51	.61	−0.25	.09
Quartile 3: 9.7 to <18.4 (n = 659)	1.70	.60	−0.29	.20
Quartile 4: ≥18.4 (n = 659)	1.93	.82	−0.42	.81
Continuous, per SD increase (13.31)	2.05	.64	−0.34	.08

Abbreviations: SD, standard deviation. SaO_2, oxygen saturation.

[a]Models adjusted by age, site, race (white vs nonwhite), body mass index, education, number of depressive symptoms, history of diabetes, history of stroke or TIA, history of hypertension, history of CHD, history of Parkinson's disease, presence of impairment of instrumental activities of daily living, benzodiazepine use, antidepressant use, self-reported health status, physical activity, alcohol use and smoking status.

Table 4

Adjusted[a] Association of Sleep Disordered Breathing Parameter and Clinically Significant Cognitive Decline

	Trails B (sec)	3MS Score
Predictor	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
Apnea-hypopnea index, events/h		
<15 (n = 1,504, reference)	1.00	1.00
≥15 (n = 1,132)	1.14 (0.84, 1.54)	0.99 (0.79, 1.24)
Continuous, per 5-unit increase	1.01 (0.96, 1.07)	1.01 (0.97, 1.05)
Oxygen desaturation index, events/h		
<15 (n = 1,219, reference)	1.00	1.00
≥15 (n = 1,417)	1.05 (0.78, 1.43)	0.95 (0.75, 1.19)
Continuous, per 5-unit increase	1.02 (0.97, 1.06)	1.01 (0.98, 1.04)
Sleep time with SaO_2 <90%, %		
<1 (n = 1,284, reference)	1.00	1.00
≥1 (n = 1,352)	0.93 (0.68, 1.27)	1.13 (0.90, 1.43)
Continuous, per SD increase (9.45)	0.91 (0.76, 1.10)	1.06 (0.95, 1.18)
Sleep time in apnea or hypopnea, %		
Quartile 1: <4.6 (n = 659, reference)	1.00	1.00
Quartile 2: 4.6 to <9.7 (n = 659)	0.88 (0.58, 1.33)	0.90 (0.66, 1.22)
Quartile 3: 9.7 to <18.4 (n = 659)	1.15 (0.77, 1.73)	0.85 (0.62, 1.17)
Quartile 4: ≥18.4 (n = 659)	0.96 (0.63, 1.46)	0.90 (0.65, 1.23)
Continuous, per SD increase (13.31)	1.05 (0.91, 1.22)	1.01 (0.91, 1.13)

Abbreviations: SD, standard deviation. SaO_2, oxygen saturation.

[a]Models adjusted by age, site, race (white vs nonwhite), body mass index, education, number of depressive symptoms, history of diabetes, history of stroke or TIA, history of hypertension, history of CHD, history of Parkinson's disease, presence of impairment of instrumental activities of daily living, benzodiazepine use, antidepressant use, self-reported health status, physical activity, alcohol use and smoking status.