

Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly

A Longitudinal Study

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Abstract

Rationale: Recent evidence suggests that obstructive sleep apnea (OSA) may be a risk factor for developing mild cognitive impairment and Alzheimer's disease. However, how sleep apnea affects longitudinal risk for Alzheimer's disease is less well understood.

Objectives: To test the hypothesis that there is an association between severity of OSA and longitudinal increase in amyloid burden in cognitively normal elderly.

Methods: Data were derived from a 2-year prospective longitudinal study that sampled community-dwelling healthy cognitively normal elderly. Subjects were healthy volunteers between the ages of 55 and 90, were nondepressed, and had a consensus clinical diagnosis of cognitively normal. Cerebrospinal fluid amyloid β was measured using ELISA. Subjects received Pittsburgh compound B positron emission tomography scans following standardized procedures. Monitoring of OSA was completed using a home sleep recording device.

Measurements and Main Results: We found that severity of OSA indices (AHIall [$F_{1,88} = 4.26; P < 0.05$] and AHI4% [$F_{1,87} = 4.36; P < 0.05$]) were associated with annual rate of change of cerebrospinal fluid amyloid β_{42} using linear regression after adjusting for age, sex, body mass index, and apolipoprotein E4 status. AHIall and AHI4% were not associated with increases in AD_{PiB}-mask (Alzheimer's disease vulnerable regions of interest Pittsburgh compound B positron emission tomography mask) most likely because of the small sample size, although there was a trend for AHIall ($F_{1,28} = 2.96, P = 0.09$; and $F_{1,28} = 2.32$, not significant, respectively).

Conclusions: In a sample of cognitively normal elderly, OSA was associated with markers of increased amyloid burden over the 2-year follow-up. Sleep fragmentation and/or intermittent hypoxia from OSA are likely candidate mechanisms. If confirmed, clinical interventions for OSA may be useful in preventing amyloid build-up in cognitively normal elderly.

Keywords: obstructive sleep apnea; amyloid burden; Pittsburgh compound B positron emission tomography scan; cerebrospinal fluid amyloid β ; cognitive impairment

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At a Glance Commentary

Scientific Knowledge on the

Subject: Recent literature in both mice and humans suggests that disturbed sleep leads to higher levels of brain soluble β amyloid peptides, which aggregate to form senile plaques, a hallmark of Alzheimer's disease. This pathologic process might be present before cognitive decline, indicating that disturbed sleep can be both a consequence of and a risk factor for Alzheimer's disease.

What This Study Adds to the

Field: This longitudinal study shows that obstructive sleep apnea, very common in elderly, can be a risk factor for developing Alzheimer's disease.

Obstructive sleep apnea (OSA) and Alzheimer's disease (AD) are chronic disease conditions that are highly prevalent, cause significant morbidity and mortality to those afflicted (1, 2), and have an enormous socioeconomic impact. OSA is typified by recurrent partial or complete obstructions of the upper airway during sleep leading to intermittent hypoxia and/or sleep fragmentation. OSA is associated with hypertension, cardiovascular risk, cognitive decline (3), and multiple inflammatory and metabolic effects (4–6) (for a review, see Reference 7). OSA affects 30–80% of the elderly (8, 9) depending on how OSA is defined. The clinical relevance of these high rates in the elderly is unclear, because some studies demonstrate increased rates of mortality, whereas others suggest that sleepiness, cognitive impairment, hypertension, and mortality associated with OSA decline with age (10). However, in a recent study of older women where

nocturnal polysomnography was collected at baseline and cognition was evaluated 5 years later, patients with OSA were more likely to develop mild cognitive impairment (MCI) or dementia at follow-up (3). In a similar study using the Alzheimer's Disease Neuroimaging Initiative database, we found that reported patients with OSA had an earlier age of cognitive decline to MCI and to AD than non-OSA control subjects (11). Furthermore, in a meta-analysis of cross-sectional studies, patients with AD were five times more likely to present with OSA than cognitively unimpaired individuals of similar age (12). Although OSA could be a consequence of events in the progression of AD pathology, alternatively, OSA may precipitate AD pathogenesis. The latter would present an exciting opportunity to slow AD pathology with sleep interventions.

The link between severity of OSA and risk for AD could be mediated by an increase in amyloid deposition as a small number of cross-sectional studies suggest. Greater $A\beta$ burden using amyloid positron emission tomography (PET) globally and regionally in the precuneus has been associated with OSA severity among patients with MCI (13). We also demonstrated a trend toward decreased cerebrospinal fluid (CSF) amyloid β_{42} ($A\beta_{42}$) levels in cognitively normal apolipoprotein E4 (ApoE4)-positive carriers with OSA (14), and a recent cross-sectional study showed that patients with OSA had lower CSF $A\beta_{42}$ levels when compared with control subjects (15), suggesting that OSA might contribute to amyloid deposition and accelerate cognitive decline in those at risk for AD. However, so far it has been challenging to verify causality for these associations because OSA and AD may share common risk factors (16, 17) and neurodegenerative consequences (17) (e.g., vascular damage, hippocampal atrophy).

Based on the existing literature, the aims of this study were to use the New York

University (NYU) Center for Brain Health cohort of cognitively normal healthy elderly to investigate the cross-sectional and longitudinal associations between OSA severity and changes in CSF and PET biomarkers of AD.

Methods

NYU Cohort

The NYU cohort consists of community-dwelling healthy cognitively normal volunteers and was derived from three NIH/National Institute on Aging and one Alzheimer's Association supported studies. All subjects received medical, neurologic, and psychiatric evaluations; clinical laboratory studies; home monitoring for OSA; structural magnetic resonance imaging scans; a lumbar puncture (LP); and/or a Pittsburgh compound B (PiB) PET scan. As such, sleep complaints were not part of the inclusion or exclusion criteria of these protocols nor were subjects referred to the studies from any sleep disorders clinic. All subjects were administered a standard neuropsychological test battery that has published norm values (18).

Subjects

Subjects were between the ages of 55 and 90, English speaking, with a minimum of 12 years of education, had Mini-Mental State Exam (19) scores between 25 and 30 (inclusive), a Clinical Dementia Rating (20) of 0, were nondepressed, and had a consensus clinical diagnosis of cognitively normal. Because of known CSF batch variations, only values that were either batch corrected or from the same assay date were included. Individuals using continuous positive airway pressure (CPAP) or with significant medical conditions that could affect brain structure or function and/or magnetic resonance imaging evidence of intracranial mass or infarcts were excluded. Written informed consent was obtained from all participants.

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Sleep Evaluation

The sleep evaluation included a sleep interview, detailed snoring history, and self-administration of the Epworth Sleepiness Scale (21). Home monitoring of OSA was completed using either an ARES Unicorder (Watermark) (22) or an Embletta MPR (Natus Medical Inc.) (23) system during a two-night period. For most subjects, home sleep evaluations were completed before the baseline LP and amyloid PET scan.

However, there were few subjects ($n = 21$) whose sleep evaluations were done after the baseline LP and amyloid PET scan. Out of these 21 subjects only five completed their follow-up LP and amyloid PET scan of whom were included in the longitudinal analyses. The variables used in this study were 1) the apnea/hypopnea index with 4% desaturation (AHI4%), defined as the sum of all apneas (>90% reduction in airflow for >10 s) and all hypopneas (>30% reduction in airflow for 10 s) associated with greater than 4% oxygen desaturation divided by the total time where both flow and oximetry signals were valid; 2) the AHIall, which was defined as the sum of all apneas and all hypopneas identified plus events with visible reduction in airflow amplitude and presence of inspiratory flattening ending in breaths with normalization of airflow as a surrogate for arousal (24), divided by the total time where there was a valid flow signal irrespective of SaO_2 ; and, 3) mean SaO_2 during the night. Although the systems used different techniques of oximetry measurement, we have previously shown that OSA indices between these two devices are highly correlated (22). Both systems and AHI indices have been compared with the recommended definitions of AHI (22). Reported total sleep time (TST) duration was assessed using one question: "During the past month, how many hours of sleep did you usually get each night?"

LP, CSF Collection, and Assays

The procedures for the NYU LP are published (25, 26). CSF amyloid β ($\text{A}\beta_{42}$), total-tau (T-tau), and tau phosphorylated at threonine 181 (P-tau) concentrations were measured using sandwich ELISA (INNOTEST). All assays were conducted at Sahlgrenska University Hospital. Batch wise rescaling of CSF $\text{A}\beta_{42}$ was performed using linear regression with a reference batch. Before rescaling $\text{A}\beta_{42}$, the coefficient of

variation was 20%, and was reduced to 10% after rescaling. P-tau and T-tau were not rescaled because the coefficient of variation between batches was already relatively low (9%). CSF assays were done blind to clinical or sleep data.

PiB Scans

All subjects received PiB PET scans following standardized published procedures (27). Parametric standardized uptake value ratio (SUVR) images were generated by normalizing PiB uptake by cerebellar gray matter uptake (28). PiB SUVR images were processed using automated regions of interest (ROIs) (27). These ROIs were used to sample AD-vulnerable brain regions from the PiB SUVR images, including hippocampus, inferior parietal lobule, lateral temporal lobe, medial frontal gyrus, posterior cingulate cortex/precuneus, prefrontal cortex, occipital cortex, and thalamus. The cortical PiB meta-ROI retention mask (Alzheimer's disease vulnerable regions of interest Pittsburgh compound B positron emission tomography mask; $\text{AD}_{\text{PiB-mask}}$) was created by combining amyloid-vulnerable inferior parietal lobule, lateral temporal lobe, medial frontal gyrus, posterior cingulate cortex/precuneus, and prefrontal cortex regions (29).

Statistical Analyses

Statistical analyses were performed using SPSS version 23 (SPSS, Inc.). Baseline measures between OSA groups (normal, mild, and moderate-severe) were examined based on AHI4% cutoff values (<5, 5–14.9, and ≥ 15 , respectively) using ANOVA with *post hoc* Tukey tests for continuous variables and chi-square test for categorical variables. Regression-based z-scores corrected for age, sex, race, and education, derived from our normative sample (18), were used for OSA group comparisons of cognitive variables (Logic 2, animal fluency, vegetable fluency, Boston Naming Test, Digit Symbol Substitution Test, Trails Making Test-A, and Trails Making Test-B), and for correlation analyses between annual rate of change of CSF $\text{A}\beta_{42}$ and annual change in cognitive z-scores. For comparison between OSA severity groups, univariate analysis was used after adjusting for age, sex, body mass index (BMI), ApoE4, and time interval between procedures.

To test whether normal elderly subjects with OSA showed evidence of positive

PET/CSF AD biomarkers, first we calculated the correlation coefficients between AD biomarkers and OSA indices at cross-section. Direct and partial correlations were computed, the latter adjusting for relevant cofactors, such as age, sex, BMI, and ApoE4 status. A similar approach was used for longitudinal analyses using Δ in amyloid biomarkers. We decided to control for these factors *a priori* given the well-documented association between decreased levels of CSF $\text{A}\beta_{42}$, old age, and presence of the ApoE4 allele. Male sex and obesity were similarly included because they are the most important risk factors for OSA, whereas female sex is also a well-known risk factor for AD.

To calculate the annual rate of change of CSF $\text{A}\beta_{42}$ or $\text{AD}_{\text{PiB-mask}}$ for each subject, we used the change in outcome from baseline to follow-up divided by the elapsed time from baseline to follow-up. We then applied a hierarchical linear regression, with annual rate of change of CSF $\text{A}\beta_{42}$ or $\text{AD}_{\text{PiB-mask}}$ as dependent variables and OSA indices as independent, adjusting first for age, sex, BMI, and ApoE4 status. To control for the type of sleep recording device, we included it as a covariate in the model. Because of the skewness and heavy tails in the distributions of $\text{AD}_{\text{PiB-mask}}$, nonparametric correlations were performed for comparisons between $\text{AD}_{\text{PiB-mask}}$ and OSA indices. Logarithm transformations were applied to continuous measures of $\text{A}\beta_{42}$, P-tau, T-tau, $\Delta \text{AD}_{\text{PiB-mask}}$, and AHI indices because of their right-skewed distributions. All statistical analyses were tested for violations of the model assumptions and any conflicts and resolutions are reported. Statistical significance was set at P less than 0.05 using two-sided tests.

Results

Baseline Demographics and Sleep Characteristics

Baseline demographic and raw values of sleep characteristics are summarized in Table 1. Among the 208 participants, 97 were free of OSA (AHI4% <5) and considered healthy control subjects, 76 had mild OSA (AHI4% 5–14.9), and 35 had moderate to severe OSA (AHI4% ≥ 15). Within the moderate to severe group only, 14 subjects had an AHI4% greater than 30 and six subjects had an AHI4% greater than 45. Patients with OSA were more

Table 1. Baseline Demographic and Sleep Characteristics of the Subjects

Characteristics	All	Normal	Mild OSA	Moderate–Severe OSA
Participants, <i>n</i> (%)	208 (100)	97 (46.63)	76 (36.53)	35 (16.82)
Female sex, <i>n</i> (%)	129 (62)	67 (69.1)	44 (57.9)	18 (51.4)
BMI, kg/m ² , median (IQR)	25.79 (22.7–29.87)	24.61 (22.32–28.17)*	26.89 (23.32–29.9)	29.76 (23.49–33.51)*
Age, yr, mean ± SD	68.46 ± 7.38	67.56 ± 7.32	68.60 ± 7.19	70.68 ± 7.69
Education, yr, median (IQR)	17 (16–18)	16.5 (16–18)	17 (16–18)	16 (14–19)
Hypertension, <i>n</i> (%)	86 (41.3)	34 (35.1)	32 (42.1)	20 (57.1)
Diabetes, <i>n</i> (%)	12 (5.8)	4 (4.1)	4 (5.3)	4 (11.4)
Cardiovascular disease, <i>n</i> (%)	9 (4.3)	1 (1)	7 (9.2)	1 (2.9)
Thyroid disease, <i>n</i> (%)	34 (16.3)	16 (16.5)	11 (14.5)	7 (20)
ApoE4 positive, <i>n</i> (%)	71 (34.1)	34 (35.1)	25 (32.9)	12 (34.3)
AHI4%, median (IQR)	5 (1.55–11.40)	1.45 (0.725–3.00)*	7.75 (5.81–10.52)*	25.00 (19.3–37.00)*
AHIall, median (IQR)	17 (10.85–24.00)	10.40 (6.75–13.65)*	20.05 (17.05–24.00)*	39.00 (31–57)*
Mean SaO ₂ , median (IQR)	94.19 (93.15–95.6)	94.57 (93.78–95.6)*	94.9 (92.77–95.71)*†	93.47 (92.1–94.5)*†
ESS, median (IQR)	5 (3–8)	4 (3–7)	6 (3.5–8.5)	6 (4–9)
TST, h, median (IQR)	7 (6.5–8)	7.48 (6.75–8)	7.00 (6.5–8)	7.50 (6.5–8)

Definition of abbreviations: AHI4% = sum of all apneas and hypopneas associated with greater than 4% oxygen desaturation; AHIall = sum of all apneas, hypopneas, or arousals; ApoE4 = apolipoprotein E4; BMI = body mass index; ESS = Epworth Sleepiness Scale; IQR = interquartile range; OSA = obstructive sleep apnea; TST = total sleep time.

*Statistically significant difference between the groups.

†Statistically significant difference between mild OSA and moderate–severe OSA groups for mean SaO₂.

commonly male and older ($\chi^2[2, n = 208] = 4.26, P = 0.11$, and $F_{2,205} = 2.36, P = 0.09$, respectively), and had significantly higher BMI than healthy control subjects ($F_{2,206} = 9.67; P < 0.01$). However it was not an obese group (mean BMI, 26.68 ± 5.35 ; only 14 subjects of the 208 with a BMI > 35). Moreover, using repeated measures ANOVA, BMI within subjects did not change significantly at follow-up ($F_{1,105} = 0.68$, not significant [NS]). We did not find significant differences across healthy control subjects and OSA groups in years of education, hypertension, diabetes, cardiovascular, thyroid disease, or ApoE4 status. Excessive daytime sleepiness was remarkably low in the entire sample (median Epworth Sleepiness Scale of 5; interquartile range, 3.8), with only 19 subjects with an Epworth Sleepiness Scale greater than 10. On univariate analysis there were no significant differences between OSA groups regarding TST. Overall TST was 7.03 ± 1.12 hours.

Psychometric Assessment

Cross-sectional and longitudinal cognitive characteristics of all subjects are shown in Table 2. We did not find any statistically significant differences between OSA indices and cognition across healthy and OSA groups at baseline or longitudinally. To assess the relationship between longitudinal changes in CSF A β_{42} and cognitive performance, we performed Pearson

correlation analyses comparing annual rate of change of CSF A β_{42} and annual change in cognitive z-scores. No statistically significant correlations were found: Logic 2 ($r = -0.12$, NS), animal fluency ($r = 0.15$, NS), vegetable fluency ($r = 0.09$, NS), Boston Naming Test ($r = 0.006$, NS), Digit Symbol Substitution Test ($r = 0.16$, NS), Trails Making Test-A ($r = 0.001$, NS), and Trails Making Test-B ($r = -0.08$, NS).

CSF and PET Assessment

From the 208 participants, 179 subjects performed an LP at baseline. A second LP was obtained at follow-up in 104 subjects 2.42 \pm 0.88 years later. A total of 86 subjects performed PiB scans at baseline. A second PiB scan evaluation was obtained at follow-up in 34 subjects 2.50 \pm 0.39 years later. A total of 57 participants performed both the LP and the PET scans at baseline. Twenty-five participants performed the LP and PET scans at both baseline and follow-up. We refer to participants with both baseline and follow-up biomarker data available as “completers,” whereas subjects with only baseline biomarkers data are referred to as “noncompleters.” There were no differences between completers and noncompleters in terms of age ($t = -0.27$, NS), sex ($\chi^2 = 0.002$, NS), BMI ($t = 0.40$, NS), Mini-Mental State Exam ($t = 0.00$, NS), years of education ($t = 0.17$, NS), ApoE4 status ($\chi^2 = 0.93$, NS), TST ($t = 1.18$, NS), AHIall ($t = 0.82$, NS), or AHI4%

($t = 0.88$, NS). Summary statistics of baseline, and annual changes of AD biomarkers are shown in Table 3. No significant associations were observed between annual changes in CSF A β_{42} and age ($F_{1,93} = 2.23; P = 0.13; \beta = -1.68$; 95% confidence interval [CI], -0.39 to $0.55; P = 0.13$), sex ($F_{1,93} = 0.64; P = 0.42; \beta = 13.64$; 95% CI, -20.17 to $47.47; P = 0.42$), BMI ($F_{1,93} = 0.16; P = 0.69; \beta = -0.61$; 95% CI, -3.67 to $2.44; P = 0.69$) or ApoE4 ($F_{1,93} = 0.42; P = 0.51; \beta = -11.35$; 95% CI, -46.03 to $23.32; P = 0.51$). At cross-section and longitudinally, we did not find any significant differences among the three OSA severity groups for CSF P-tau or T-tau. Similarly, no cross-sectional or longitudinal effects were found for CSF A β_{42} across OSA severity groups using univariate analysis. No significant correlation between CSF A β_{42} and AHI indices were observed at cross-section.

However, significant correlations were observed between longitudinal change in CSF A β_{42} levels and AHIall/AHI4% ($r = -0.24, P < 0.05$; and $r = -0.23, P < 0.05$, respectively) and after controlling for age, sex, BMI, and ApoE4 ($r = -0.27, P < 0.05$; and $r = -0.24, P < 0.05$, respectively). Significant associations were also observed between annual rate of change of CSF A β_{42} and AHI indices at baseline using hierarchical linear regression model (shown in Table 4), including annual rate of change of CSF A β_{42} as dependent and

Table 2. Cognitive Characteristics of NYU Cohort at Baseline and Follow-up Evaluations

	All (n = 108)	Normal (n = 50)	Mild OSA (n = 43)	Moderate–Severe OSA (n = 15)
MMSE baseline	29.31 ± 0.99	29.40 ± 0.93	29.18 ± 0.98	29.33 ± 1.30
MMSE follow-up	29.36 ± 0.85	29.51 ± 0.718	29.29 ± 0.867	29.00 ± 1.206
CDR baseline	0 ± 0	0 ± 0	0 ± 0	0 ± 0
CDR follow-up	0.010 ± 0.071	0 ± 0	0 ± 0	0.083 ± 0.19
Animal fluency (z-scores)	0.207 ± 0.99	0.24 ± 1.14	0.05 ± 0.81	0.50 ± 0.95
Animal fluency (Δ z-scores)	−0.23 ± 0.87	−0.30 ± 0.98	−0.20 ± 0.85	−0.11 ± 0.54
Vegetable fluency (z-scores)	−0.042 ± 1.1	−0.023 ± 0.98	−0.14 ± 1.28	0.15 ± 0.96
Vegetable fluency (Δ z-scores)	−0.14 ± 0.99	−0.39 ± 0.87	0.087 ± 1.08	−0.02 ± 0.98
Boston Naming Test (z-scores)	−0.20 ± 1.03	−0.10 ± 1.06	−0.38 ± 0.98	−0.017 ± 1.07
Boston Naming Test (Δ z-scores)	0.11 ± 0.71	0.24 ± 0.69	0.12 ± 0.71	−0.28 ± 0.69
Logic 1 (z-scores)	0.19 ± 0.96	0.11 ± 1.0	0.24 ± 0.90	0.29 ± 1.05
Logic 1 (Δ z-scores)	−0.007 ± 0.86	−0.03 ± 0.87	−0.07 ± 0.82	0.23 ± 0.96
Logic 2 (z-scores)	0.10 ± 1.0	0.11 ± 1.07	0.008 ± 0.97	0.33 ± 0.88
Logic 2 (Δ z-scores)	−0.012 ± 0.75	0.042 ± 0.8	−0.06 ± 0.75	−0.04 ± 0.67
Trails Making Test-A time (z-scores)	0.062 ± 1.06	−0.14 ± 0.88	−0.33 ± 1.04	0.12 ± 0.89
Trails Making Test-A time (Δ z-scores)	0.048 ± 0.88	0.025 ± 0.14	0.127 ± 0.7	−0.093 ± 1.03
Trails Making Test-B time (z-scores)	−0.17 ± 0.96	−0.14 ± 0.89	−0.33 ± 1.04	0.12 ± 0.9
Trails Making Test-B time (Δ z-scores)	−0.034 ± 0.72	−0.007 ± 0.65	−0.002 ± 0.63	−0.19 ± 0.64
DSST (z-scores)	0.2 ± 0.95	0.2 ± 0.83	0.14 ± 1.03	0.36 ± 1.11
DSST (Δ z-scores)	0.07 ± 0.44	0.1 ± 0.44	−0.003 ± 0.45	0.18 ± 0.37

Definition of abbreviations: CDR = Clinical Dementia Rating; DSST = Digit Symbol Substitution Test; MMSE = Mini-Mental State Exam; NYU = New York University; OSA = obstructive sleep apnea.

Data are shown as mean ± SD.

Lower z-scores represent worse cognitive function.

AHI indices (lnAHI4% and lnAHIall) as independent variables, before ($F_{1,92} = 5.41$, $P < 0.05$; and $F_{1,93} = 4.72$, $P < 0.05$, respectively) and after accounting for age, sex, BMI, and ApoE4 ($F_{1,88} = 4.26$, $P < 0.05$; and $F_{1,87} = 4.36$, $P < 0.05$, respectively). The effect of the type of sleep recording device and TST were not significant, thus we excluded them from the final model. Figure 1 shows the relationship between Δ in CSF $A\beta_{42}$ and the AHI indices at baseline. Sensitivity analyses were performed excluding five subjects whose baseline sleep evaluation was done after their first CSF measurements. Association between lnAHI4%, lnAHIall, and annual Δ CSF $A\beta_{42}$ remained unchanged.

Similarly, on univariate analysis no difference in AD_{PiB}-mask was observed between OSA severity groups, and no significant correlation between AD_{PiB}-mask and AHI indices were observed at cross-section. However, correlations were observed between longitudinal change in AD_{PiB}-mask and AHIall or AHI4% ($r = 0.374$, $P < 0.05$; and $r = 0.302$, $P = 0.09$, respectively) after controlling for age, sex, BMI, and ApoE4. Using the same hierarchical linear regression model as for CSF $A\beta_{42}$, no statistically significant associations were observed between annual rate of change of AD_{PiB}-mask and

AHIs, including annual rate of change of AD_{PiB}-mask as dependent and AHI indices at baseline as independent variables after accounting for age, sex, BMI, and ApoE4. lnAHIall and lnAHI4% were not associated with increases in AD_{PiB}-mask most likely because of the small sample size because there was a trend for lnAHIall ($F_{1,28} = 2.96$, $P = 0.09$; and $F_{1,28} = 2.32$, NS, respectively). Figure 2 shows the relationship between Δ in AD_{PiB}-mask and the AHIall index at baseline; both variables were corrected for normal distribution by log transformation.

Furthermore, we analyzed the association between longitudinal change in CSF $A\beta_{42}$ and AD_{PiB}-mask. Using a Pearson correlation, a significant negative correlation between longitudinal change in CSF $A\beta_{42}$ and AD_{PiB}-mask was observed ($r = -0.44$; $P < 0.05$). Using an AD_{PiB}-mask SUVR greater than or equal to 1.4 to define presence of brain amyloid deposition (PiB-positive) (30–32), a secondary analysis performed only in the initial cross-sectional cases, revealed a significant difference between the slopes of PiB-positive and PiB-negative cases (Figure 3). This was confirmed by the presence of an interaction between PiB status and lnAHI4% ($F_{1,29} = 5.54$; $P < 0.05$) and a positive trend between AHI4% and PiB uptake in

PiB-positive subjects ($r = 0.67$; $P = 0.07$). Similar findings were observed for AHIall (data not shown). Figure 3 shows the relationships between the AHI4% and PiB SUVR uptake when comparing PiB-positive with PiB-negative groups.

Discussion

The primary objective of this study was to determine if severity of OSA in cognitively normal elderly is associated with CSF and PET AD biomarkers at cross-section and their longitudinal change across an approximate 2-year period. Our initial finding revealed that OSA was common and affected 53% of our cognitively normal community-dwelling cohort. Second, we demonstrated that baseline OSA severity was associated with 2-year longitudinal decreases in CSF $A\beta_{42}$ and a trend toward increases in cortical PiB-PET uptake. Such changes are potentially consistent with increased brain amyloid burden, which were also observed in our cohort (i.e., a negative correlation between longitudinal change in CSF $A\beta_{42}$ and AD_{PiB}-mask), suggesting that OSA may play a role in amyloid deposition in late-life. Moreover, the magnitude of these changes was higher than the one predicted by the presence of

Table 3. Alzheimer's Disease Biomarker Characteristics

	All (n = 208)	Normal (n = 97)	Mild OSA (n = 76)	Moderate-Severe OSA (n = 35)
CSF A β ₄₂ baseline (n = 179), mean \pm SD	681.31 \pm 236.43	681.88 \pm 243.18	690.61 \pm 233.99	657.48 \pm 224.79
CSF A β ₄₂ annual change (n = 104), median (IQR)	29.40 (-9.53 to 71.06)	40.59 (4.23 to 80.80)	26.97 (-29.99 to 66.71)	-4.088 (-18.97 to 27.92)
CSF P-tau baseline (n = 179), median (IQR)	41 (31 to 52)	42.50 (31.5 to 52.05)	43.55 (30 to 55)	40.97 (31.71 to 49)
CSF P-tau annual change (n = 104), mean \pm SD	1.42 \pm 3.93	1.35 \pm 3.18	0.73 \pm 4.27	3.43 \pm 4.90
CSF T-tau baseline (n = 179), median (IQR)	257.96 (202 to 360.91)	268.04 (217.65 to 362)	244.85 (198 to 382)	248.14 (174 to 343)
CSF T-tau annual change (n = 104), mean \pm SD	8.24 \pm 21.42	7.52 \pm 18.86	5.85 \pm 21.83	17.04 \pm 27.53
AD _{PiB} PET mask baseline (n = 86), median (IQR)	1.05 (1.02 to 1.11)	1.047 (1.02 to 1.09)	1.061 (1.00 to 1.11)	1.06 (1.01 to 1.14)
AD _{PiB} PET mask annual change (n = 34), median (IQR)	0.0005 (-0.009 to 0.014)	-0.0020 (-0.0095 to 0.0078)	-0.0022 (-0.0126 to 0.0224)	0.014 (0.006 to 0.028)

Definition of abbreviations: A β ₄₂ = amyloid B₄₂; AD_{PiB} PET mask = Alzheimer's disease vulnerable regions of interest Pittsburgh compound B PET mask; CSF = cerebrospinal fluid; IQR = interquartile range; OSA = obstructive sleep apnea; PET = positron emission tomography; P-tau = tau phosphorylated at threonine 181; T-tau = total tau.

Table 4. Final Model Showing Relationship of Annual Δ CSF $A\beta_{42}$ and Annual Δ PiB with AHIall and AHI4%

Dependent variable	Models	R^2	ΔR^2	Independent Variables	β	95% CI	P Value
Annual Δ CSF $A\beta_{42}$	Model	-0.008	0.035	Age	-1.36	-3.67 to 0.95	0.24
				Sex	6.63	-27.72 to 40.99	0.70
				BMI	0.88	-2.36 to 4.12	0.59
				ApoE4	-15.54	-50.69 to 8.81	0.36
	Model + AHI4%*	0.028	0.046	AHI4%	-13.35	-26.06 to -0.64	0.04
Annual Δ PiB	Model	-0.068	0.062	Age	0.001	-0.001 to 0.004	0.28
				Sex	0.001	-0.036 to 0.038	0.96
				BMI	-0.001	-0.004 to 0.002	0.37
				ApoE4	0.01	-0.026 to 0.046	0.36
	Model + AHI4%	0.134	0.072	AHI4%	0.013	-0.004 to 0.03	0.13
Annual Δ CSF $A\beta_{42}$	Model	-0.008	0.035	Age	-1.57	-3.86 to 0.70	0.17
				Sex	4.07	-30.36 to 38.51	0.81
				BMI	1.0	-2.27 to 4.27	0.54
				ApoE4	-17.89	-52.58 to 16.79	0.30
	Model + AHIall	0.027	0.044	AHIall	-29.08	-57.08 to -1.08	0.04
Annual Δ PiB	Model	-0.068	0.062	Age	0.001	-0.001 to 0.004	0.25
				Sex	0.001	-0.036 to 0.038	0.96
				BMI	-0.001	-0.004 to 0.002	0.37
				ApoE4	0.01	-0.026 to 0.046	0.56
	Model + AHIall	0.151	0.09	AHIall	0.026	-0.05 to 0.057	0.09

Definition of abbreviations: $A\beta_{42}$ = amyloid β_{42} ; AHI = apnea-hypopnea index; AHI4% = the sum of all apneas and hypopneas associated with greater than 4% oxygen desaturation; AHIall = the sum of all apneas, hypopneas, or arousals; ApoE4 = apolipoprotein E4; BMI = body mass index; CI = confidence interval; CSF = cerebrospinal fluid; PiB = Pittsburgh compound B.

*AHI4% is missing in 1 subject owing to errors in home sleep pulse oximetry measurements.

the ApoE4 allele alone (Table 4), which to date is considered the most important risk factor for sporadic AD. AHIall, which includes hypopneas associated with oxygen desaturation or arousals, was a better

predictor of longitudinal increases in amyloid burden than AHI4%, which includes only hypopneas associated with 4% oxygen desaturation. This raises the possibility that sleep fragmentation is a

more critical pathophysiologic mechanism by which OSA contributes to AD risk. However, AHIall and AHI4% were highly correlated in our cohort ($r = 0.91$; $P < 0.01$) and this study was unable to differentiate

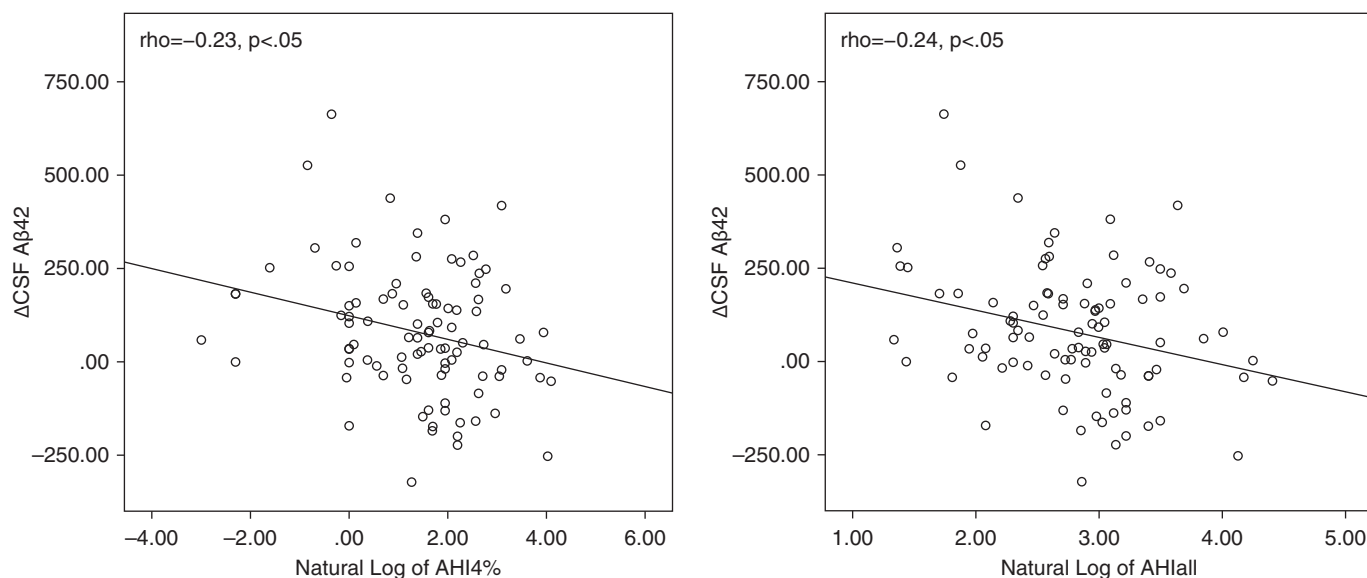


Figure 1. Relationship between longitudinal change in cerebrospinal fluid amyloid β_{42} ($A\beta_{42}$) and the natural log of apnea-hypopnea indices at baseline. AHI = apnea-hypopnea index; AHI4% = sum of all apneas and hypopneas associated with greater than 4% oxygen desaturation; AHIall = sum of all apneas, hypopneas, or arousals; CSF = cerebrospinal fluid.

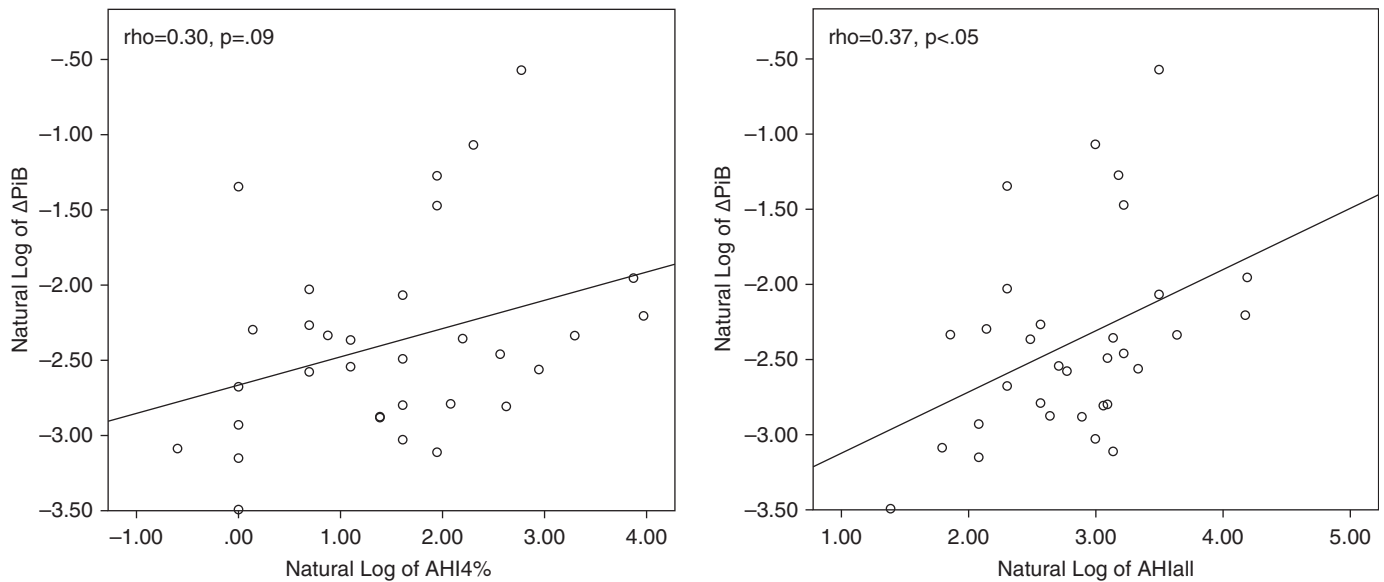


Figure 2. Relationship between longitudinal change in $AD_{PiB\text{-mask}}$ and the apnea–hypopnea indices at baseline. $AD_{PiB\text{-mask}}$ = Alzheimer’s disease vulnerable regions of interest Pittsburgh compound B positron emission tomography mask; AHI = apnea–hypopnea index; AHI4% = sum of all apneas and hypopneas associated with greater than 4% oxygen desaturation; AHIall = sum of all apneas, hypopneas, or arousals; PiB = Pittsburgh compound B.

the individual effects of sleep fragmentation versus intermittent hypoxia.

Although OSA severity was associated with increases in brain amyloid burden, it was not predictive of cognitive deterioration based on neuropsychological performance, which is in agreement with prior studies (33, 34). This is not completely surprising given that the relationship between amyloid

burden and cognition is probably nonlinear and dependent on additional factors, such as tau pathology and microvascular changes. Low sensitivity of the neuropsychological tests used may have been another factor. Sensitivity could be increased in the future by using cognitive tasks that are known to be sleep dependent.

Current evidence suggests that cognitive decline in AD is associated with decreases in CSF $A\beta_{42}$ and increases in amyloid PET uptake (35). However, little is known about the temporal course of CSF $A\beta_{42}$ in the preclinical or early stages of the disease, with some recent animal and human studies showing $A\beta_{42}$ elevations before $A\beta_{42}$ reductions (36, 37), suggesting an intermediate stage of increased soluble $A\beta$ levels before amyloid deposition. Interestingly, we and others have shown that reduced slow wave activity at cross-section and one night of slow wave sleep (SWS) disruption, are associated with increases in CSF $A\beta$ levels, potentially as a consequence of increases in neuronal firing and/or decreases in amyloid clearance (38–41). It remains to be determined how universal a period of elevated CSF $A\beta_{42}$ in humans is observed before a decline, but the previously mentioned studies suggest that sleep disruption might be associated with elevations of CSF $A\beta_{42}$, which in chronic sleep disorders, such as OSA, could foster its aggregation and manifest as longitudinal decreases in CSF $A\beta_{42}$ over time, such as the one observed in our study. This hypothesis would also explain the absence of significant associations at cross-section.

Whether OSA-related sleep fragmentation increases AD-risk through disruption of SWS or other sleep stages is

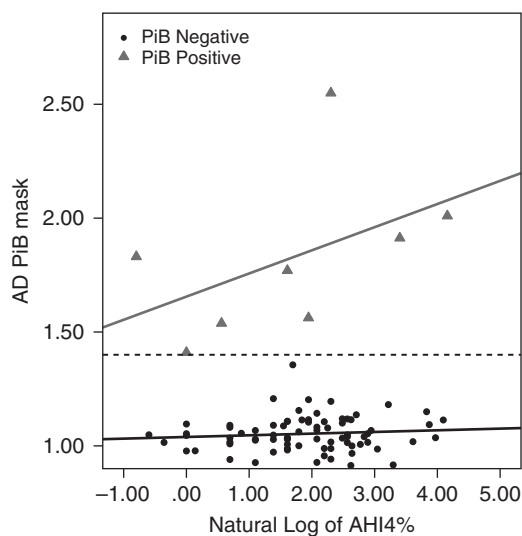


Figure 3. At cross-section, severity of obstructive sleep apnea is associated with greater brain amyloid β deposition in PiB-positive participants, whereas no such association is found in participants with PiB-negative scans. $AD_{PiB\text{ mask}}$ = Alzheimer’s disease vulnerable regions of interest Pittsburgh compound B positron emission tomography mask; AHI4% = sum of all apneas and hypopneas associated with greater than 4% oxygen desaturation; PiB = Pittsburgh compound B.

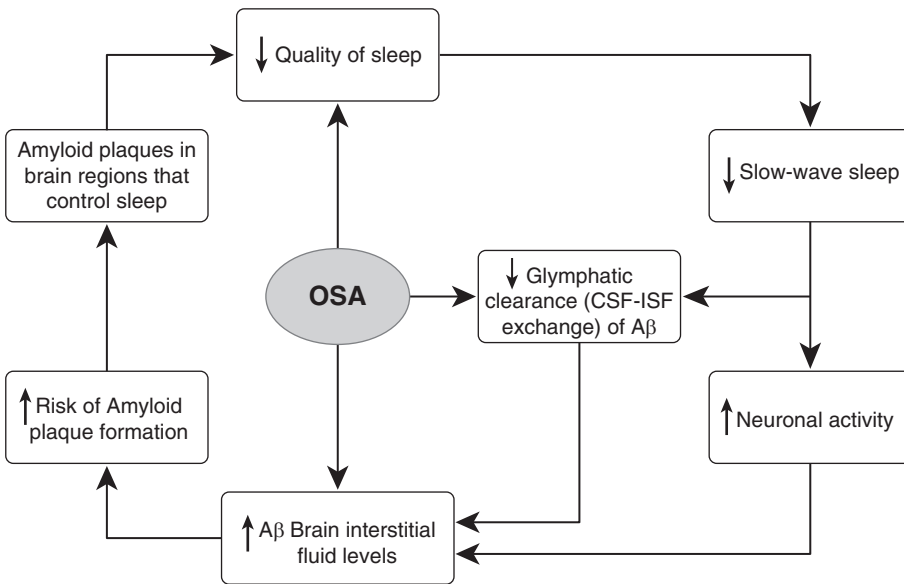


Figure 4. Obstructive sleep apnea-related arousals may worsen sleep quality and increase amyloid deposition in a feed-forward cycle. Aβ = amyloid β; CSF = cerebrospinal fluid; ISF = interstitial fluid; OSA = obstructive sleep apnea.

unknown. The ends of apneas are associated with arousals or awakenings that prevent sleep (42) and these are more commonly observed in non-REM1–2 and REM sleep. Apneic episodes are less common in SWS, which has been associated with a higher respiratory arousal threshold (43, 44) and more stable breathing (45). However, the temporal course of slow wave activity has been shown to be slower in mild OSA (46), whereas severe patients with OSA show up to a 40% rebound in SWS duration during

OSA treatment with CPAP (47), which suggest that changes in SWS quality may also be involved. However, a recent prospective study reported the association between decreased percentage of REM sleep and increased risk of dementia, implicating also REM sleep as a possible mediator for AD risk (48). In addition, actigraphy-assessed arousals and circadian rhythm disruption have also been shown to increase the risk of MCI/dementia in the elderly (49), indicating that the relationship

between OSA-related sleep fragmentation and amyloid deposition might not be stage-specific.

Another possible mechanism by which OSA might increase amyloid deposition is through impairment in the CSF–interstitial fluid (ISF) exchange promoted by the glymphatic system (40) resulting in decreased clearance of ISF Aβ₄₂. This mechanism was suggested in a recent study of 31 control subjects and 10 severe OSA middle-age subjects where neuronally derived proteins were decreased in the OSA group when compared with control subjects (40). The authors propose that elevations in the intrathoracic and intracranial pressure as well as a sudden pressure reversal at the end of the apnea would impede the glymphatic flow of metabolites from ISF into CSF (40). Another potential pathway of impairment of CSF–ISF exchange could be cerebral edema secondary to intermittent hypoxia, as proposed recently in a study in which severity of OSA correlated with increased volume and thickness of the left lateral prefrontal cortex and increased thickness of the right frontal pole, the right lateral parietal lobules, and the left posterior cingulate cortex (50). Similar findings were observed as brain volume reductions after 6 months of treatment with CPAP, which also suggests the existence of brain edema in OSA (51).

Finally, the effects of OSA directly increasing ISF Aβ₄₂ burden as suggested by some intermittent hypoxia animals models (52, 53), or indirectly through other intermediate mechanisms, such as oxidative stress, sympathetic activation, inflammation, hypercoagulability, endothelial dysfunction, or metabolic dysregulation, cannot be discarded, although it is feasible that these and other consequences of OSA may decline with age (10, 54) and might not be as relevant in the elderly as in middle age.

Among participants with initial PiB-positive scans at cross-section, Figure 3 suggest that a higher severity of OSA is associated with greater brain Aβ deposition, whereas no such association is found in participants with PiB-negative scans, implying that presence or absence of amyloid burden might act as a moderator in these relationships. This would be in agreement with previous studies showing increased amyloid deposition associated with higher AHI indices in patients with MCI but not in cognitively normal control

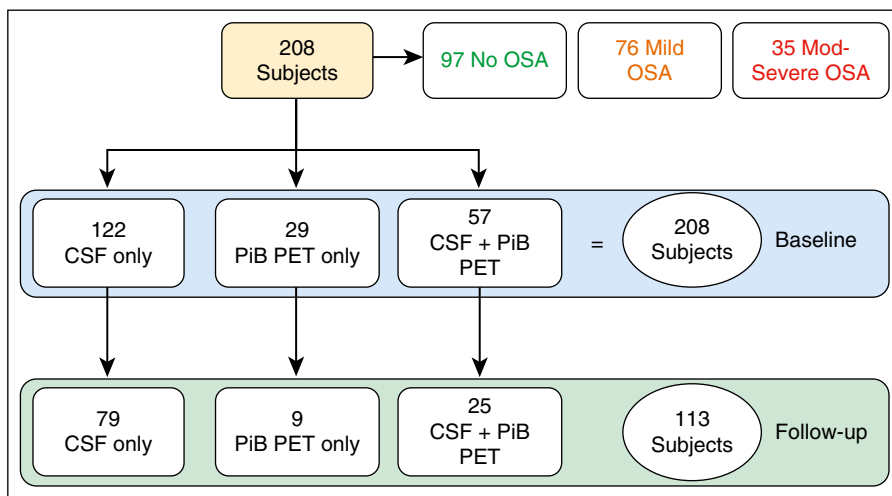


Figure 5. Breakdown of completers and noncompleters. CSF = cerebrospinal fluid; Mod = moderate; OSA = obstructive sleep apnea; PET = positron emission tomography; PiB = Pittsburgh compound B.

subjects at cross-section (13). We did not observe this effect in the CSF sample when we compared amyloid-positive with amyloid-negative cases based on the NYU Center for Brain Health CSF bank A β_{42} cutoffs (i.e., CSF A β_{42} ng/ml <500), so this finding should be interpreted with caution. It may be that the effects of OSA/hypoxia on A β aggregation are most pronounced after significant A β accumulation has already occurred, leading to an acceleration of further A β deposition in a feed-forward cycle (13) (Figure 4) with OSA-related arousals worsening sleep quality and increasing amyloid deposition. In addition, 33 of 34 of the subjects that had PiB PET follow-up scans were PiB-negative at baseline, indicating that the observed longitudinal increases in PiB uptake were not dependent on amyloid status.

Our observations are consistent with our hypothesis that there is an association between severity of OSA-related sleep fragmentation and longitudinal increase in amyloid burden in cognitively normal elderly. This implies that existing therapies for OSA, such as CPAP, could delay the progression to MCI or dementia in elderly with OSA, as was suggested by our previous epidemiologic studies using the Alzheimer's Disease Neuroimaging Initiative database (11) and a recent cross-sectional study in

which patients with OSA showed lower CSF A β_{42} concentrations, and higher T-tau/A β_{42} ratio when compared with patients with OSA-CPAP (15).

The high prevalence of mild and moderate-to-severe OSA in cognitively normal elderly in asymptomatic adults undergoing screening for OSA as part of a protocol on memory and normal aging adds to the importance of these findings. Strengths of our study include that our community-residing subjects were not recruited for the study based on sleep complaints, and thus should have been free of selection biases potentially affecting sleep clinic-based cohorts, which typically include younger, more frequently male, obese, and symptomatic (e.g., excessive daytime sleepiness, treatment-resistant hypertension). We also used state-of-the-art methods for home-monitoring of OSA, and longitudinal standardized CSF and PET biomarkers. Potential weaknesses of the study were the relative short duration and the lack of longitudinal sleep data, which did not allow us to test whether preclinical-AD brain lesions increase the risk for OSA, or the lack of a longer clinical assessment to test whether amyloid deposition is followed by cognitive decline to MCI or AD. Another limitation of the study was that not all subjects

had a longitudinal follow-up, although both completers and noncompleters (Figure 5) were not different in terms of sociodemographics, BMI, Mini-Mental State Exam, AHIall, or AHI4%.

In summary, to our knowledge this study is the first to document that OSA is associated with longitudinal changes in amyloid burden in a sample of cognitively normal elderly. The implication of these findings is that we have identified a contribution of OSA in increasing the A β burden before significant cognitive decline occurs. Our data support testing whether clinical interventions aimed at OSA, such as treatment with CPAP or dental appliances, could be implemented during the early phase in which tissue damage precedes clinical symptoms and neuronal dysfunction, to mitigate the progression of cognitive impairment. ■

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