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.

Objective: 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 was 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 to 90, were non-depressed and had a consensus clinical diagnosis of cognitively normal. CSF Amyloid beta 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 (lnAHIall [$F_{1,88}$=4.26, p<.05] and lnAHI4% [$F_{1,87}$=4.36, p<.05]) were associated with annual rate of change of CSF $A\beta_{42}$ using linear regression after adjusting for age, sex, BMI and ApoE4 status. LnAHIall and lnAHI4 were not associated with increases in AD_{PiB}-mask most likely due to the small sample size although there was a trend for lnAHIall ($F_{1,28}$=2.96, p=.09 and $F_{1,28}$=2.32, n.s. respectively).

Conclusion: 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.

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 beta amyloid peptides, which aggregates to forms senile plaques, a hallmark of Alzheimer's disease. This pathological process might be present prior to cognitive decline, indicating that disturbed sleep can be both a consequence 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.

INTRODUCTION:

Obstructive Sleep Apnea (OSA) and Alzheimer's disease (AD) are both chronic disease conditions that are highly prevalent, cause significant morbidity and mortality to those afflicted,[1;2] and have an enormous socio-economic 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[7]). OSA affects up to 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, as some studies demonstrate increased rates of mortality, while 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, OSA patients 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 (ADNI) database, we found that reported OSA patients had an earlier age of cognitive decline to MCI and to AD than non-OSA controls.[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] While 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 Aβ burden using amyloid-PET, globally and regionally in the precuneus has been associated with OSA severity among MCI patients.[13] We also demonstrated a trend toward decreased cerebrospinal fluid (CSF) amyloid beta 42 (Aβ42) levels in cognitively normal ApoE4+ carriers with OSA,[14] and a recent cross-sectional study showed that OSA patients had lower CSF Aβ42 levels when compared to controls,[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 as OSA and AD may share common risk factors[16;17] as well as neurodegenerative consequences[17] (*e.g.* vascular damage, hippocampal atrophy).

Based on the existing literature, the aims of this study were to use the NYU Center for Brain Health (CBH) 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 3 NIH/NIA and 1 Alzheimer's Association supported studies. All subjects received medical, neurological, and psychiatric evaluations, clinical labs, home monitoring for OSA, structural magnetic resonance imaging (MRI) 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 which has published norm values.[18]

Subjects:

Subjects were between the ages of 55 to 90, English speaking, with a minimum of 12 years of education, had Mini-Mental State Exam (MMSE)[19] scores between 25–30 (inclusive), a Clinical Dementia Rating (CDR)[20] of 0, were non-depressed and had a consensus clinical diagnosis of

cognitively normal. Due to 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 MRI evidence of intracranial mass or infarcts were excluded. Written informed consent was obtained from all participants.

Sleep Evaluation:

The sleep evaluation included a sleep interview, detailed snoring history, and self-administration of the Epworth Sleepiness Scale (ESS).[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 2-night period. For most subjects, home sleep evaluations were completed prior to the baseline lumbar puncture (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 5 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 sec) and all hypopneas (>30% reduction in airflow for 10 sec) associated with >4% oxygen (O_2) 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 O_2 saturation; and, (3) mean saturation of oxygen (O_2Sat) 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?"

Lumbar Puncture, CSF Collection and assays:

The procedures for the NYU lumbar puncture (LP) are published.[25;26] CSF amyloid beta ($A\beta_{42}$), total-tau (T-tau) and tau phosphorylated at threonine 181 (P-tau) concentrations were measured using sandwich enzyme-linked immunosorbent assays (*INNOTEST, Belgium*). All assays were conducted at Sahlgrenska University Hospital. Batch wise rescaling of CSF $A\beta_{42}$ was performed using linear regression with a reference batch. Before rescaling $A\beta_{42}$, the coefficient of variation (CV) was 20%, and was reduced to 10% after rescaling. P-tau or T-Tau were not rescaled because the CV 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 grey matter uptake.[28] PiB SUVR images were processed using automated regions-of-interest (ROI).[27] These ROIs were used to sample AD-vulnerable brain regions from the PiB SUVR images, including: hippocampus (Hip), inferior parietal lobule (IPL), lateral temporal lobe (LTL), medial frontal gyrus (MFG), posterior cingulate cortex/precuneus (PCC), prefrontal cortex (PFC), occipital cortex (OCC), and thalamus (Thal). The cortical PiB meta-ROI retention mask (AD_{PiB}-mask) was created by combining amyloid-vulnerable IPL, LTL, MFG, PCC, and PFC regions.[29]

Statistical analyses:

Statistical analyses were performed using SPSS (*version 23, SPSS, Inc., Chicago, IL*). 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 [AF], Vegetable Fluency [VF]), Boston Naming Test [BNT], Digit Symbol Substitution Test [DSST], Trails Making Test-A [TMT-A] and Trails Making Test-B [TMT-B]); as well as for correlation analyses between annual rate of change of CSF $A\beta_{42}$ and annual change in cognitive z-scores. For comparison between OSA severity groups, univariate analysis was used after adjusting for age, sex, 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 delta change in amyloid biomarkers. We decided to control for these factors a priori given the well documented association between decreased levels of CSF Aβ42, old age and the presence of ApoE4 allele. Male sex and obesity were similarly included as they are the most important risk factors for OSA, while female sex is also a well-known risk factor for AD.

To calculate the annual rate of change of CSF $A\beta_{42}$ or AD_{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 Aβ42 or ADPiB-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. Due to the skewness and heavy tails in the distributions of AD_{PIB}-mask, non-parametric correlations were performed for comparisons between AD_{PiB}-mask and OSA indices. Logarithm transformations were applied to continuous measures of $A\beta_{42}$, P-Tau, T-Tau, delta AD_{PiB}-mask and AHI indices due to 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<.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 controls, 76 had mild OSA (AHI4% 5-15), and 35 had moderate to severe OSA (AHI4%>15). Within the moderate to severe group only, 14 subjects had an AHI4%>30 and 6 subjects had an AHI4%>45. OSA patients were more commonly male and older [X^2 (2,n=208)=4.26, p=.11, $F_{2,205}$=2.36, p=0.09 respectively] and had significantly higher BMI than healthy controls ($F_{2,206}$=9.67, p<.01). However it was not an obese group (mean BMI of 26.68±5.35 and 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 ($F_{1,105}$=.68, n.s.). We did not find significant differences across healthy controls and OSA groups in years of education, hypertension, diabetes, cardiovascular, thyroid disease or ApoE4 status. Excessive daytime sleepiness (EDS) was remarkably low in the entire sample (median ESS of 5, IQR 3,8), with only 19 subjects with an ESS>10. On univariate analysis there were no significant differences between OSA groups regarding TST. Overall TST was 7.03±1.12 hrs.

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 $A\beta_{42}$ and cognitive performance, we performed Pearson correlation analyses comparing annual rate of change of CSF Aβ42 and annual change in cognitive z-scores. No statistically significant correlations were found: Logic 2 (r=-.12, n.s.), AF (r=.15, n.s.), VF (r=.09, n.s.), BNT (r=.006, n.s.), DSST (r=.16, n.s.), TMT-A (r=.001, n.s.) and TMT-B (r=-.08, n.s.).

CSF and PET Assessment:

From the 208 participants, 179 subjects performed a lumbar puncture (LP) at baseline. A second LP was obtained at follow-up in 104 subjects 2.42±0.88 years later. 86 subjects performed PiB scans at baseline. A second PiB scan evaluation was obtained at follow-up in 34 subjects 2.50±0.39 years later. 57 participants performed both the LP and the PET scans at baseline. 25 participants performed the LP and PET scans at both baseline and follow-up (Figure 5). We will refer to participants with both baseline and follow-up biomarker data available as "*completers",* whereas subjects with only baseline biomarkers data will be referred to as "*non-completers"*. There were no differences between *completers* and *non-completers,* in terms of (age [t=-.27, n.s.], sex [X^2=.002, n.s.], BMI [t=.40, n.s.], MMSE [t=.00, n.s.], years of education [t=.17, n.s.], ApoE4 status [X^2=.93, n.s.], TST [t=1.18, n.s.], AHIall [t=.82, n.s.] or AHI4% [t=.88, n.s.]). 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 $A\beta_{42}$ and age ($F_{1,93}$=2.23, p=.13, β=-1.68, 95% Confidence Interval [CI]= -.39 to .55, p=.13), sex ($F_{1,93}$=.64, p=.42, β=13.64, 95% CI = -20.17 to 47.47, p=.42), BMI ($F_{1,93}$=.16, p=.69, β=-.61, 95% CI=-3.67 to 2.44, p=.69) or ApoE4 ($F_{1,93}$=.42, p=.51, β=-11.35, 95% CI= -46.03 to 23.32, p=.51). At cross-section and longitudinally, we did not find any significant differences among the 3 OSA severity groups for CSF P-Tau or T-Tau. Similarly, no cross-sectional or longitudinal effects were found for CSF $A\beta_{42}$ across OSA severity groups using univariate analysis. No significant correlation between CSF $A\beta_{42}$ and AHI indices were observed at cross-section.

However, significant correlations were observed between longitudinal change in CSF $A\beta_{42}$ levels and AHIall/AHI4 (rho=-0.24, p<.05, rho=-0.23, p<.05, respectively) and after controlling for age, sex, BMI and ApoE4 (rho=-0.27, p<.05, rho=-0.24, p<.05, respectively). Significant associations were also observed between annual rate of change of CSF $A\beta_{42}$ and AHI indices at baseline using hierarchical linear regression model (shown in table 4), including annual rate of change of CSF $A\beta_{42}$ as dependent and AHI indices (lnAHI4 and lnAHIall) as independent variables, before ($F_{1,92}$=5.41, p<.05, and $F_{1,93}$=4.72, p<.05 respectively) and after accounting for age, sex, BMI and ApoE4 ($F_{1,88}$=4.26, p<.05 and $F_{1,87}$=4.36, p<.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 delta change in CSF $A\beta_{42}$ and the AHI indices at baseline. Sensitivity analyses were perfomed excluding 5 subjects whose baseline sleep evaluation was done after their first CSF measurements. Association between lnAHI4, lnAHIall, and annual delta CSF Aβ42 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 (rho=0.374, p<.05, rho=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 due to the small sample size as there was a trend for lnAHIall ($F_{1,28}$=2.96, p=.09 and $F_{1, 28}$=2.32, n.s. respectively). Figure 2 shows the relationship between delta change in AD_{PiB}-mask and the AHIall index at baseline, both variables were corrected for normal distribution by log transformation.

Further, 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=-.44, p<.05). Using an AD_{PiB}-mask SUVR ≥1.4 to define presence of brain amyloid deposition (PiB+),[30-32] a secondary analysis performed only in the initial cross-sectional cases, revealed a significant difference between the slopes of PiB+ and PiB- cases (Figure 3). This was confirmed by the presence of an interaction between PiB status and lnAHI4% ($F_{1,29}$=5.54, p<.05) as well as a positive trend between AHI4% and PiB uptake in PiB+ subjects (rho=0.67, p=.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+ vs. PiB- 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 two-year longitudinal decreases in CSF $A\beta_{42}$ and a trend towards 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 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 pathophysiological mechanism by which OSA contributes to AD risk. However, AHIall and AHI4% were highly correlated in our cohort (r=0.91, p<.01) and this study was unable to differentiate 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 employing 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 prior to $A\beta_{42}$ reductions,[36;37] suggesting an intermediate stage of increased soluble Aβ levels prior to amyloid deposition. Interestingly, we and others have shown that reduced slow wave activity (SWA) at cross-section as well as one night of SWS disruption,

are associated with increases in CSF Aβ 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 prior to a decline, but the above 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 unknown. The ends of apneas are associated with arousals or awakenings that prevent sleep[42] and these are more commonly observed in NREM1-2 and REM sleep. Apneic episodes are less common in SWS, which has been associated with a higher respiratory arousal threshold[43;44] as well as more stable breathing.[45] However, the temporal course of SWA has been shown to be slower in mild OSA,[46] while severe OSA patients 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-ISF exchange promoted by the glymphatic system[40] resulting in decreased clearance of ISF $A\beta_{42}$. This mechanism was suggested in a recent study of 31 controls and 10 severe OSA middle-age subjects where neuronally derived proteins were decreased in the OSA group when compared to controls.[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 as well as 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 six months of treatment with CPAP which also suggests the existence of brain edema in OSA.[51]

Finally, the effects of OSA directly increasing ISF $A\beta_{42}$ 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+ scans at cross-section, Figure 3 suggest that a higher severity of OSA is associated with greater brain Aβ deposition, while no such association is found in participants with PiB- 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 MCI patients but not in cognitively normal controls at cross-section.[13] We did not observe this effect in the CSF sample when we compared *amyloid* positive *vs.* negative cases based on the NYU CBH CSF bank $A\beta_{42}$ cut-offs (*i.e.* CSF $A\beta_{42}$ ng/ml <500), so this finding should be interpreted with caution. It may be that the effects of OSA/hypoxia on Aβ aggregation are most pronounced after significant Aβ

accumulation has already occurred, leading to an acceleration of further Aβ deposition in a feed–forward cycle[13] (Figure 4) with OSA-related arousals worsening sleep quality and increasing amyloid deposition. In addition, 33/34 of the subjects that had PiB PET follow-up scans were PiB- 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 epidemiological studies using the ADNI database[11] and a recent cross-sectional study in which OSA patients showed lower CSF $A\beta_{42}$ concentrations, as well as higher T-tau/$A\beta_{42}$ ratio when compared to OSA-CPAP patients.[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, etc.). We also utilized a state-of-the-art method for home-monitoring of OSA, as well as 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 *non-completers* were not different in terms of sociodemographics, BMI, MMSE, 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 amyloid beta burden prior to significant cognitive decline. 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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Tables

Table 1: Baseline demographic and sleep characteristics of the subjects

Characteristics	All	Normal	Mild OSA	Moderate-Severe OSA
No. of Participants (%)	208 (100)	97 (46.63)	76 (36.53)	35 (16.82)
Female sex, number (%)	129 (62)	67 (69.1)	44 (57.9)	18 (51.4)

BMI (Kg/m2), 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, years, mean ± SD	68.46 ± 7.38	67.56 ± 7.32	68.60 ± 7.19	70.68 ± 7.69
Education, years, median (IQR)	17 (16, 18)	16.5 (16,18)	17 (16,18)	16 (14,19)
Hypertension, number (%)	86 (41.3)	34 (35.1)	32 (42.1)	20 (57.1)
Diabetes, number (%)	12 (5.8)	4 (4.1)	4 (5.3)	4 (11.4)
Cardiovascular disease, number (%)	9 (4.3)	1 (1)	7 (9.2)	1 (2.9)
Thyroid disease, number (%)	34 (16.3)	16 (16.5)	11 (14.5)	7 (20)
APOE4 positive, number (%)	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 O2 Saturation, median (IQR)	94.19 (93.15, 95.6)	94.57 (93.78,95.6)*	94.9 (92.77,95.71)a	93.47 (92.1,94.5)* a
ESS, median (IQR)	5 (3,8)	4 (3,7)	6 (3.5,8.5)	6 (4,9)
TST,hours, median (IQR)	7 (6.5, 8)	7.48 (6.75,8)	7.00 (6.5,8)	7.50 (6.5,8)

*,a Statistical significant difference between the groups.

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(mean±SD)	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 (delta change 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 (delta change 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 (delta change 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 (delta change 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 (delta change 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 (delta change z-scores)	0.048±0.88	0.025±0.14	0.127±0.7	-.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 (delta change 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(delta change z-scores)	0.07±0.44	0.1±0.44	-.003±.45	0.18±0.37

462 *Statistical significant difference between the groups. Lower scores represent worse cognitive function.

Table 3: AD Biomarker characteristics

	ALL (n=208)	Normal (n=97)	Mild OSA (n=76)	Moderate-Severe OSA (n=35)
CSF Aβ42 baseline (n=179) Mean ± SD	681.31 ±236.43	681.88 ± 243.18	690.61 ± 233.99	657.48 ± 224.79
CSF Aβ42 annual change (n=104) Median (Interquartile range)	29.40 (-9.53,71.06)	40.59 (4.23,80.80)	26.97 (-29.99,66.71)	-4.088 (-18.97,27.92)
CSF P-tau baseline (n=179) Median (Interquartile range)	41 (31,52)	42.50 (31.5,52.05)	43.55 (30,55)	40.97 (31.71,49)
CSF P-tau annual change (n=104) Mean ± SD	1.42 ± 3.93	1.35 ± 3.18	0.73 ± 4.27	3.43 ± 4.90
CSF T-tau baseline (n=179) Median (Interquartile range)	257.96 (202,360.91)	268.04 (217.65,362)	244.85 (198,382)	248.14 (174,343)
CSF T-tau annual change (n=104) Mean ± SD	8.24 ± 21.42	7.52 ± 18.86	5.85 ± 21.83	17.04 ± 27.53
AD_{PiB} PET baseline (n=86) Median (Interquartile range)	1.05 (1.02,1.11)	1.047 (1.02,1.09)	1.061 (1.00,1.11)	1.06 (1.01,1.14)
AD_{PiB} PET annual change (n=34) Median (Interquartile range)	0.0005 (-0.009,0.014)	-0.0020 (-0.0095,0.0078)	-0.0022 (-0.0126,0.0224)	0.014 (0.006,0.028)

463 *Statistical significant difference between the groups.

Dependent variable		R^2	ΔR^2	Independent variables	B	95% CI	p
Annual ΔCSF Aβ42	Model 1	-.008	.035	Age	-1.36	-3.67, .95	.24
				Sex	6.63	-27.72, 40.99	.70
				BMI	.88	-2.36, 4.12	.59
				ApoE4	-15.54	-50.69, 8.81	.36
	Model 1 +AHI4	.028	.046	AHI4	-13.35	-26.06, -.64	.04
	Model 1	-.008	.035	Age	-1.57	-3.86, .70	.17
				Sex	4.07	-30.36, 38.51	.81
				BMI	1.0	-2.27, 4.27	.54
				ApoE4	-17.89	-52.58, 16.79	.30
	Model 1 +AHIall	.027	.044	AHIall	-29.08	-57.08, -1.08	.04

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Dependent variable		R^2	ΔR^2	Independent variables	B	95% CI	p
Annual Ln ΔPiB	Model 1	-.068	.062	Age	.001	-.001, .004	.28
				Sex	.001	-.036, .038	.96

				BMI	-.001	-.004, .002	.37
				ApoE4	.01	-.026, .046	.36
	Model 1 +AHI4	.134	.072	**AHI4**	.013	-.004, .03	.13
	Model 1	-.068	.062	**Age**	.001	-.001, .004	.25
				Sex	.001	-.036, .038	.96
				BMI	-.001	-.004, .002	.37
				ApoE4	.01	-.026, .046	.56
	Model 1 +AHIall	.151	.09	**AHIall**	.026	-005, .057	.09

Table 4: Final model showing relationship of annual ΔCSF Aβ42 and annual ln ΔPiB with AHIall and AHI4%.

Figures

Figure 1

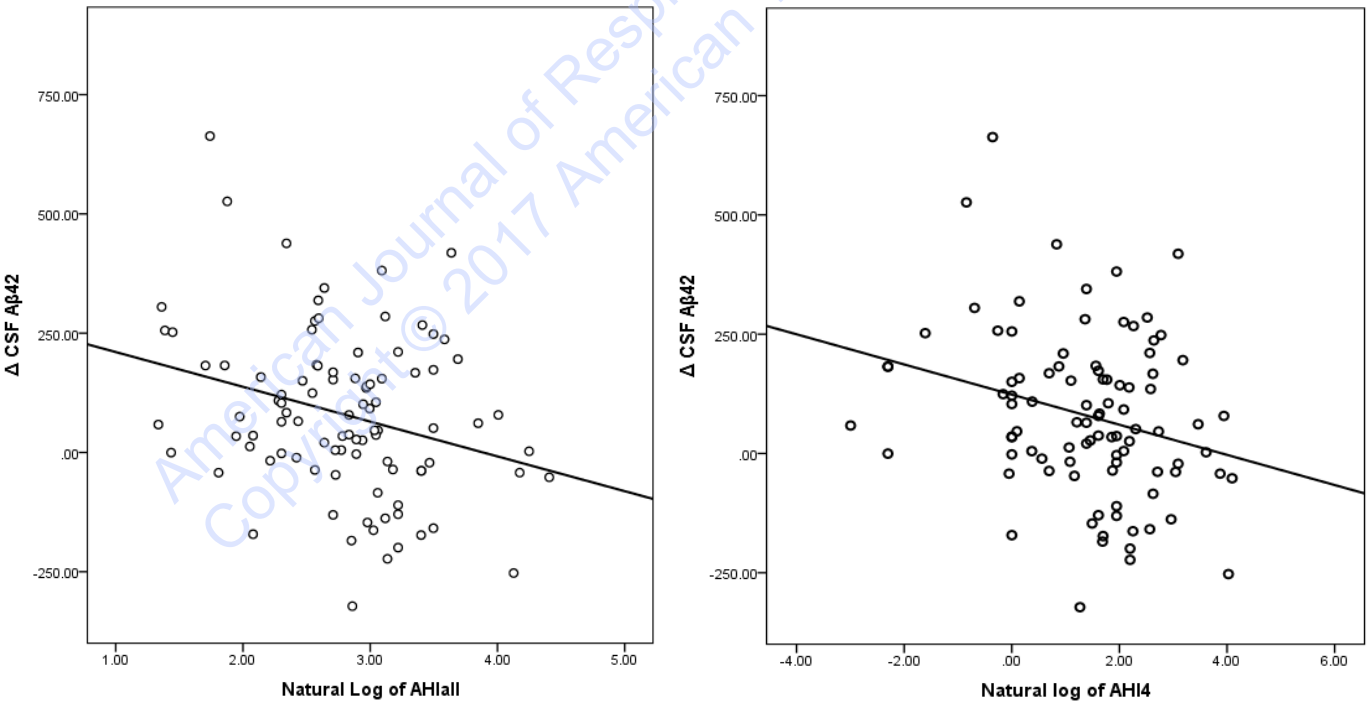


Figure 2

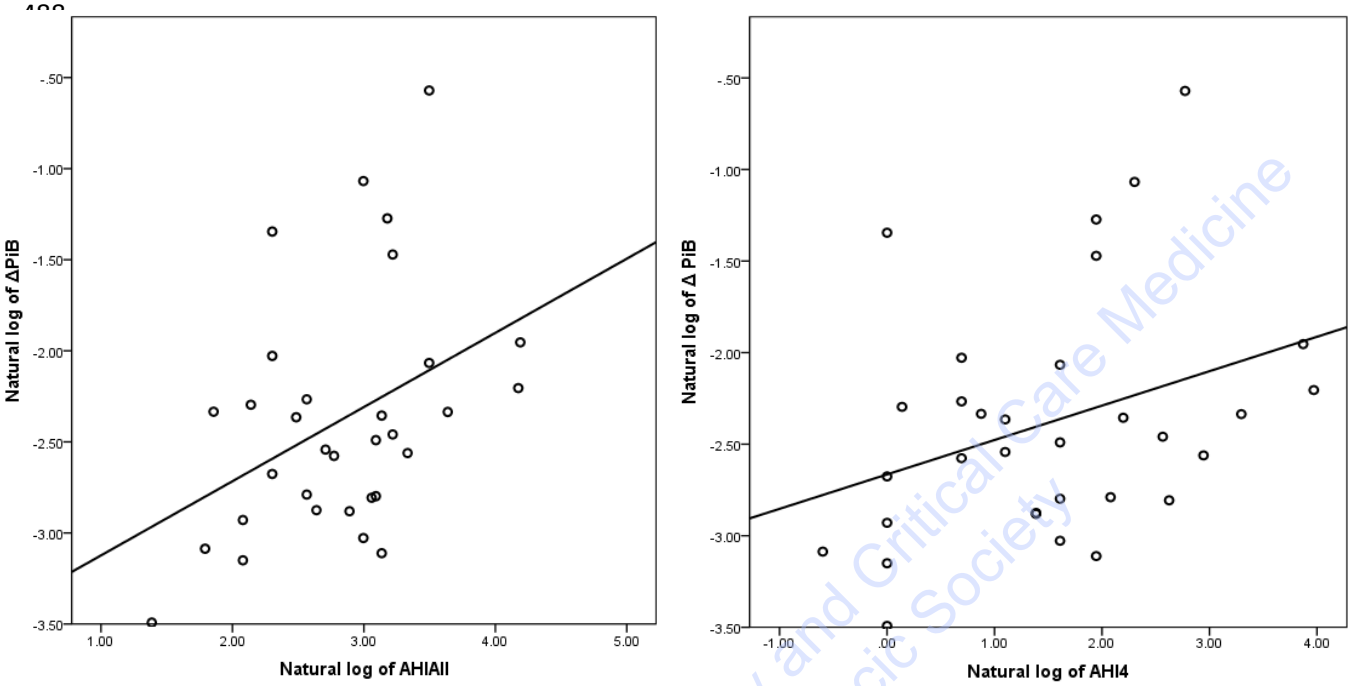


Figure 3

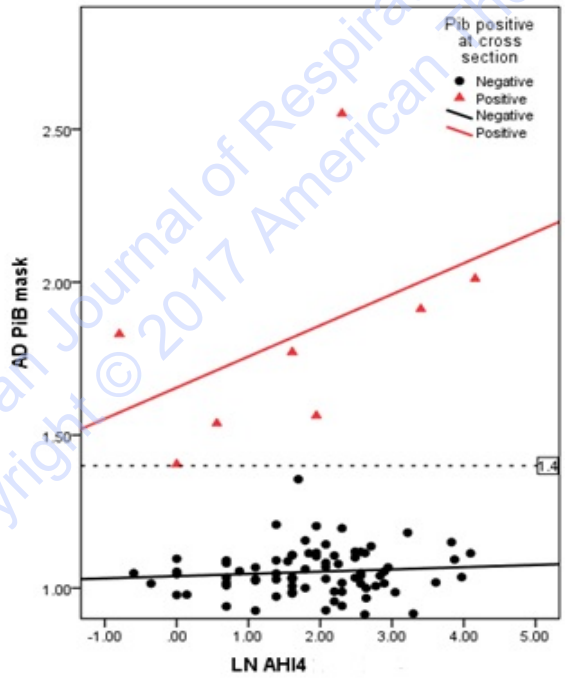


Figure 4

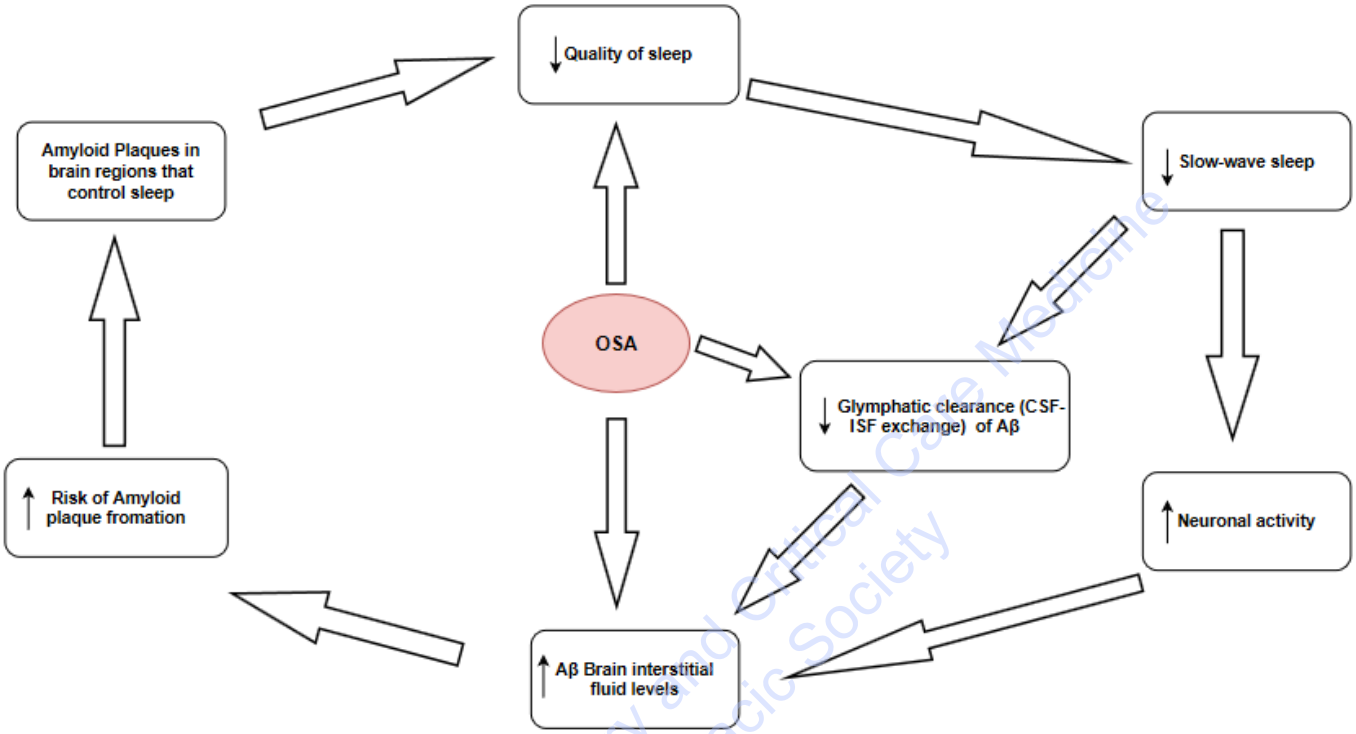
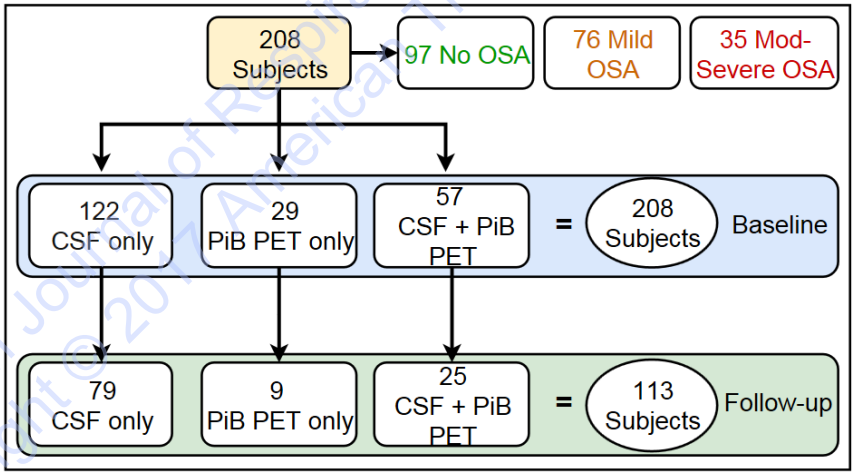


Figure 5



Study flow chart showing a detailed breakdown of subjects based on AD biomarker evaluations at the baseline and follow up visits.

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