

# Obstructive Sleep Apnea is Associated with Longitudinal Increases in Amyloid Burden in Elderly Mild Cognitive Impairment Individuals

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## ABSTRACT

Cross sectional analysis has shown an association between Obstructive Sleep Apnea (OSA) severity and A $\beta$  burden using amyloid-PET among Mild Cognitive Impairment (MCI) patients. However, whether OSA accelerates longitudinal increases in amyloid beta (A $\beta$ ) burden in MCI patients is presently unclear. Study participants included a total of 798 subjects with a diagnosis of MCI and were a subset of the ADNI cohort (adni.loni.usc.edu). OSA was self-reported and participants were labeled either as OSA+ or OSA-. A $\beta$  burden was determined by florbetapir SUVr. To test whether OSA is associated with the rate of change in A $\beta$  data longitudinally, multilevel mixed effects linear regression was used to fit the models with randomly varying intercepts and slopes allowing dependence on OSA status. The final model was adjusted for age, sex, body mass index, education, CPAP use status, history of respiratory disease, hypertension, diabetes, and history of cardiovascular disease. A significant variation in the change (slope) in A $\beta$  volumes over time was seen ( $p < .0001$ ). The covariance between the baseline A $\beta$  level and A $\beta$  volume change over time indicated that OSA subjects experienced greater mean change differences in brain A $\beta$  volumes over time ( $p < .0001$ ). The rate of change in A $\beta$  deposition also varied significantly across OSA groups over the follow-up period. Obstructive Sleep Apnea possibly facilitates longitudinal increases in amyloid burden in elderly Mild Cognitive Impairment individuals. Further research examining mechanisms underlying effects of OSA on the longitudinal increases in A $\beta$  burden is needed.

## KEYWORDS

Obstructive Sleep Apnea; OSA; Amyloid; Mild Cognitive Impairment; MCI; Elderly

## INTRODUCTION

Alzheimer's Disease (AD) and Obstructive Sleep Apnea (OSA) are both highly burdensome chronic diseases. OSA affects a predicted 23.4% of middle-aged women and 49.7% of middle-aged men, though estimates vary. The disease is associated with significant morbidity, and frequently goes undiagnosed.<sup>1</sup> AD affects an estimated 5.4 million Americans and costs \$236 billion per year to provide care.<sup>2</sup> Development of preventative measures is therefore imperative to reduce this societal burden.

Mild Cognitive Impairment (MCI) is a condition in which memory loss is beyond the scope of normal aging, but is not severe enough to meet the criteria for AD.<sup>3</sup> MCI is frequently a precursor to AD and is therefore an ideal stage for preventative intervention.<sup>3,4</sup> Factors that alter the progression from MCI to AD can be studied using biomarkers such as amyloid beta (A $\beta$ ).<sup>5</sup> A $\beta$  begins accumulating long before the onset of symptomatic AD and has been supported as a reliable marker of disease progression.<sup>6</sup>

OSA is characterized by intermittent obstruction of the upper airway during sleep resulting in hypoxia and sleep fragmentation. It is treatable using continuous positive airway pressure (CPAP). Past research has indicated a correlation between untreated OSA and cognitive decline.<sup>7,8</sup> Studies have further associated worse sleep quality with increased A $\beta$  deposition in humans.<sup>9,10</sup> Moreover, one study found the presence of OSA to be associated with the development of cognitive impairment at follow up approximately five years later.<sup>11</sup> Furthermore, a recent study demonstrated that objectively measured OSA was associated with markers of increased amyloid burden over a 2-year follow-up in the NYU cohort that consisted exclusively of community-dwelling healthy cognitively normal elderly.<sup>12</sup> However, whether OSA accelerates longitudinal increases in A $\beta$  burden in MCI patients is presently unclear.

Therefore, we hypothesized that OSA would facilitate longitudinal increases in brain amyloid beta deposition in individuals with MCI. Such a finding would consolidate understanding of the relationship between OSA and cognitive decline as well as further focus prevention efforts.

**METHODS**

*ADNI Dataset*

We downloaded data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu/>) on December 7, 2016. ADNI is a longitudinal multisite study, which seeks to confirm that MRI, PET, and other biomarker data in conjunction with clinical and neuropsychological assessment can be used measure the progression of MCI and AD. Subject data was collected through approximately 50 universities and medical centers in the United States and Canada. Follow up was performed at 6-month intervals for approximately 3 years. Each site received IRB and radiation safety committee (RSC) or radioactive approval, before scanning subjects. A written informed consent was obtained from all participants.

*Participants*

We used the subset of the cohort with mild cognitive impairment for analysis. Seven hundred and ninety-eight (798) individuals were included. The criteria for MCI classification were as follows: (i) Mini-Mental State Evaluation (MMSE) score in the range of 24-30; (ii) CDR score of 0.5 with a minimum of 0.5 on the memory box score; (iii) On one paragraph from the Logical Memory II subscale of the Wechsler Memory Scale- Revised (maximum score of 25), a minimum score of 8 for 16 years of education, 4 for 8-15 years of education, and 2 for 0-7 years of education. Additionally, MCI individuals must have had memory complaints, while largely maintaining general cognition and functional performance. They could not qualify for diagnosis of dementia. Subjects were excluded if: (i) “Insomnia” or other unspecified sleep disturbances were present, because lack of sleep has been independently associated with cognitive decline;<sup>13</sup> (ii) Past surgery to treat OSA was reported; (iii) A change in body mass index (BMI) greater than 5 between visits was observed, because BMI is independently associated with both OSA and cognitive decline;<sup>14</sup> (iv) MCI diagnosis was reversible; or (v) Data was missing for any important covariates such as APOE4 status, history of cardiovascular disease, or CPAP status.

*OSA Diagnosis*

A clinical interview was conducted with each participant in order to determine OSA status. If a participant reported a previous clinical diagnosis of “sleep apnea”, “sleep disordered breathing”, “OSA”, or “SDB”, then they were classified as OSA+. The remaining participants were classified as OSA-. To ensure correct classification, three physicians (OQU. FM. And OM.B.) reviewed the medical history clinical notes and confirmed group placement.

Characteristics	All	OSA-	OSA+
Number of participants (%)	798 (100)	695 (87)	103 (13)
Female gender, number (%)	319 (40)	297 (43)	25 (25)
Age, years, median (interquartile range)	74 (68, 79)	71 (70, 78)	71 (70, 76)
APOE positive, number (%)	410 (51)	368 (53)	42 (41)
Education, years, median (interquartile range)	16 (14, 18)	16 (14, 18)	16 (14, 18)
BMI (kg/m <sup>2</sup> )	26.9 ± 4.6	26.5 ± 4.4	29.0 ± 5.3
Hypertension, number (%)	395 (49)	337 (48)	58 (56)
Diabetes, number (%)	75 (9)	57 (8)	18 (17)
Thyroid Disease, number (%)	156 (20)	133 (19)	23 (22)
Respiratory Disease, number (%)	195 (24)	133 (19)	62 (60)
Aβ, median (interquartile range)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	1.1 (1.0, 1.3)

**Table 1:** Descriptive characteristics of MCI Participants by Obstructive Sleep Apnea status. Abbreviations: Aβ: Amyloid β; APOE: Apolipoprotein E; BMI: Body Mass Index

*Amyloid PET*

Florbetapir (18F-AV-45) PET data was obtained and processed as previously described elsewhere.<sup>15,16</sup> Briefly, images were acquired in 5-minute scans repeated four times, 50-70 minutes after florbetapir injection. Resulting images were realigned, averaged, interpolated to a common voxel size (1.5 mm<sup>3</sup>), and smoothed to a common resolution (8 mm<sup>3</sup> in full width at half maximum). Mean florbetapir standard uptake value ratios (SUVRs) were created by averaging the lateral and medial anterior frontal, posterior cingulate, lateral parietal and lateral temporal regions and then normalized to a cerebellar reference region.

*Statistical Analysis*

Analyses were performed using SAS 9.3.<sup>17</sup> All variables were plotted for assessment of outliers. Frequency distributions of all variables were also assessed. Descriptive statistics were calculated for demographic and clinical data at baseline. Characteristics of the study groups by OSA status was compared using Pearson’s Chi Squared test and for all categorical variables e.g. gender. T

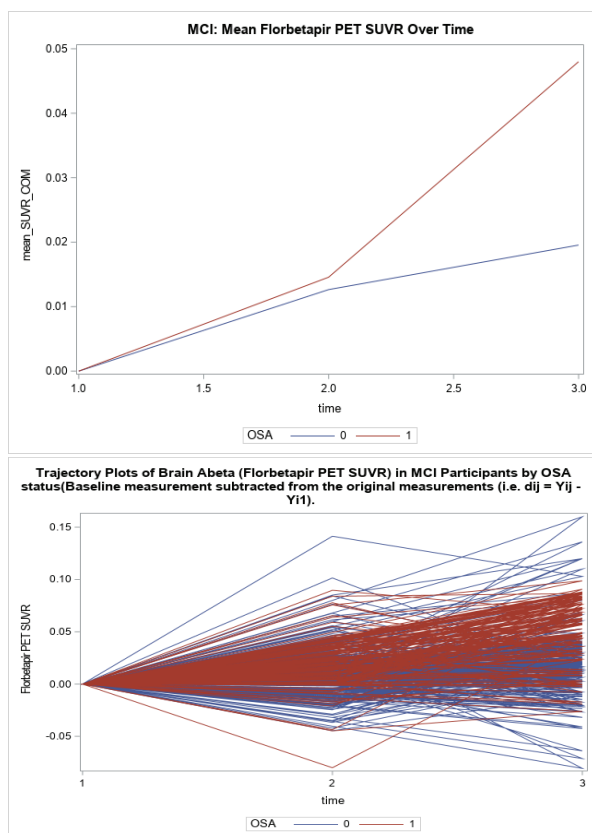
test was used for continuous variables. Bivariate analysis was conducted to describe the distribution of OSA status across categories of all potential confounders and clinical covariates e.g. age, sex. Potential confounders were identified and included in the two stage multi-level mixed effect linear regression model (described below) if exclusion or addition of a covariate to the full model caused a change in the adjusted  $A\beta$  estimates of OSA status by 10% or more.

Multivariate ANOVA was used to assess for differences in time trend groups (OSA+ vs. OSA-) and time points. The ADNI data was unbalanced with unequal numbers of measurements for each participant. Therefore, in order to minimize bias, multilevel mixed effects linear regression models with normal errors were used to analyze the rate of change of  $A\beta$  volume longitudinally based on OSA status.<sup>18-20</sup> PROC MIXED was used to fit the model with randomly varying intercept and slopes, allowing dependence on OSA status. The final model was adjusted for age, sex, body mass index, education, CPAP use, APOE e4 status, history of respiratory disease, hypertension, diabetes, history of traumatic brain injury, and history of cardiovascular disease (including ischemic heart disease, heart failure, and stroke/TIA).

Sensitivity analysis removing self-reported CPAP-users (n=16) from OSA+ participants had a negligible impact on the estimates (e.g.  $A\beta$  burden estimate of .06 changed to .08). Power issues as well as insufficient follow-up data points hindered conducting the same complex analyses comparing longitudinal changes in biomarkers between OSA patients treated by CPAP and OSA patients not under CPAP treatment.

**RESULTS**

At baseline, the median (interquartile range) age of participants was 74 (68, 79). Females accounted for 319 (40%) of the participants and the median (interquartile range) years of education was 16 (14, 18). The average BMI was  $26.5 \pm 4.4$  for those without OSA and  $29.4 \pm 5.3$  for those with OSA (Table 1).



**Figure 1.** Multivariate Analysis of Variance showing Brain  $A\beta$ -42 Differences in Time Trend, Groups (OSA+ versus OSA-) And Time-points by OSA status 0=OSA- and 1=OSA+. Y-axis: MCI: Mild Cognitive Impairment; SUVR: Standard Uptake Value Ratio of Brain Florbetapir; mean\_SUVR\_COM: Mean change Brain Florbetapir Uptake Value; Florbetapir PET SUVR: Florbetapir Positron Emission Tomography Standard Uptake Value Ratio of Brain Florbetapir Y-axis: pg/ml; X-axis: Time 1= baseline, Time 2=Year 2 value minus baseline, and Time 3= Year 3 value minus baseline.

Figure 1a-b shows results from MANOVA showing Brain Aβ-42 differences in time trend, groups (OSA+ versus OSA-) and time-points by OSA status. The MANOVA time trend of the Aβ levels showed that the change trend was not parallel across groups as shown by the group\*time interaction term (Pillai's Trace test p value=.0143). Across all subjects, the mean Aβ levels increased significantly over time. Significant differences in mean brain Aβ across OSA status existed when each time point was compared to the previous time point (time point 1 p value<.0001; time point 2 p value=.0137).

Manova Test Criteria	Statistic	Value	F-value	P-value
Timepoint* OSA Effect	Pillai's Trace	0.047	4.24	0.0143*
Timepoint Effect	Pillai's Trace	0.129	18.06	<.0001***
Repeated Measures Analysis of Variance of Contrast Variables OSA+ v OSA-				
Timepoint_1 (Year 2)			0.08	0.7786
Timepoint_2 (Year 3)			4.63	0.0323*
Timepoint_1 v timepoint_0			25.63	<.0001***
Timepoint_2 v timepoint_1			6.16	0.0137*

Table 2: Multivariate ANOVA Results Testing Biomarker Mean Change Differences in Time Trend, Groups and Time Points.

\*P-value <=.05  
 \*\*P-value <=.01  
 \*\*\*P-value<=.001

Multilevel mixed effects regression modeling showed significant variation in the change (slope) in Aβ-42 volumes over time (B=.08, 95% CI=.05, .12, p-value<.0001). The covariance between the baseline Aβ-42 level and Aβ-42 volume change over time indicated that OSA subjects experienced a faster increase in brain Aβ-42 volumes over time (B=-.06, 95% CI= -.09, -.04, p-value<.0001). The rate of change in Aβ-42 deposition also varied significantly across OSA groups over the follow-up period.

Parameters	Estimate	95% CI	P-value
OSA+ vs. OSA-			
β- Amyloid Burden at Baseline (intercept)	0.06	.03, .09	<.0001
β- Amyloid Burden over time (slope)	0.08	.05, .12	<.0001
β- Amyloid Burden over time (covariance)	-0.06	-.09, -.04	<.0001

Table 3: Between Subject Variation in β-Amyloid Deposition in Mild Cognitive Impairment.

DISCUSSION

This longitudinal study found that individuals with OSA experienced an increased rate of Aβ deposition over time (average follow-up time was 2.52 ± 0.52 years), compared to non-OSA participants.

These findings are consistent with past studies, which have indicated a cross-sectional association between OSA and Aβ and an increased incidence of AD in OSA individuals. Cross-sectionally, Spira, et al. found that sleep deprivation was correlated with increased brain Aβ levels in community dwelling older adults.<sup>10</sup> Both Bu et al and Ligouri et al found that untreated OSA was associated with AD biomarkers.<sup>21,22</sup> OSA was further found to be associated with earlier onset of AD by Osorio, et al.<sup>23</sup> In a recent meta-analysis, Bubu et al found that those with OSA were at a 2.37 times higher risk for cognitive impairment or AD.<sup>7</sup> Based on such studies it has been hypothesized that OSA may facilitate greater rate of Aβ deposition over time. To our knowledge, our study is the first to examine Aβ deposition longitudinally in OSA+ and OSA- individuals in an MCI cohort to support this hypothesis.

Past research has proposed mechanisms that may explain the increased rate of amyloid deposition that was observed. Hypoxia, a hallmark of OSA, has been shown to contribute to increases in Aβ production.<sup>24</sup> In mice, hypoxia treatment was correlated with an increased levels of brain Aβ, which indicates a potential relationship between hypoxia and AD pathogenesis.<sup>25</sup> Disruption of the sleep cycle, another characteristic of OSA, may also contribute to decreased Aβ clearance and therefore greater accumulation.<sup>26</sup> We did not specifically examine MRI measures of brain atrophy in this study, however, our findings suggest that in OSA patients, hypoxia or sleep fragmentation significantly affects brain Aβ changes, which parallels neurodegeneration that in turn may drive the rate of cognitive decline.

Strengths and Limitations

This study possesses several strengths including a well-defined cohort, and objective assessment of β-amyloid burden, which allowed for a high degree of certainty regarding measurement of our outcome. In addition, our statistical analytic methods were robust with respect to unbalanced number of observations per subject over time.

A limitation of this study is the self-reported nature of OSA. Self-reported sleep measures can be influenced by cognitive deficits and in certain situations might not be correlated with objective sleep measurements.<sup>27,28</sup> Furthermore, reported OSA prevalence in our cohort was lower than the OSA prevalence in the elderly population suggested by epidemiological and sleep laboratory

studies. This can relate to an underdiagnosis effect and most likely indicates that some OSA+ individuals were incorrectly categorized as OSA-. Most likely, such an error would have driven our findings towards the null. However, one implication of OSA classification by self-report is that those who sought diagnosis most likely did so because they were experiencing associated symptoms. The prevalence of OSA in our cohort (6%) is similar to the U.S. prevalence of OSA Syndrome (4%), which is defined by both AHI  $\geq 5$  and daytime symptoms (i.e. excessive daytime sleepiness).<sup>29</sup> The prevalence of OSA with or without symptoms in the elderly is much higher (estimated at 30-50% in older subjects).<sup>30</sup> This is significant because the associated symptoms of OSA may also impact A $\beta$  accumulation. Notably, all-cause excessive daytime sleepiness in elderly subjects defined by Epworth sleepiness scores  $\geq 10$  was associated with longitudinal brain beta amyloid accumulation in a recent study.<sup>31</sup> Therefore, additional work may be required to differentiate the risk of OSA for AD with and without associated daytime symptoms

Our results have potentially significant public health implications. Since the majority of OSA goes undiagnosed, our findings further highlight the need for increased screening and treatment of obstructive sleep apnea. Individuals with mild cognitive impairment are an especially high priority for intervention, as OSA treatment could potentially slow their cognitive decline. Controlled intervention trials are needed to confirm the efficacy of OSA treatment (i.e. CPAP) in reversing the increased rate of A $\beta$  deposition.

## CONCLUSIONS

A faster rate of amyloid beta deposition was seen in individuals with obstructive sleep apnea compared to non-OSA participants. Further studies are needed to replicate this finding using more objective sleep measures. In MCI elderly, clinical interventions aimed to treat OSA are needed to test if OSA treatment can affect the progression of cognitive impairment due to AD.

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#### ABOUT STUDENT AUTHORS

Megan Hogan and Amanda Shim will both graduate in 2019 with a B.S. in Applied Health Science. After graduating, Megan will pursue a master’s degree in physician assistant studies and Amanda plans to attend medical school.

**PRESS SUMMARY**

Obstructive sleep apnea (OSA) is a highly prevalent, treatable, and frequently undiagnosed disease in the United States today. OSA has previously been cross-sectionally associated with a hallmark of Alzheimer’s Disease—amyloid beta burden in the brain. Whether this relationship can be seen longitudinally has remained unclear. In this study, the amyloid beta levels of 798 subjects were tracked over about three years as a part of the Alzheimer’s Disease Neuroimaging Initiative. Amyloid beta accumulated at a faster rate in subjects with OSA as compared to controls. This indicates that OSA could be facilitating cognitive decline. If so, then OSA is a possible target for therapeutic intervention for slowing progression to Alzheimer’s Disease. Further research replicating these findings using objective sleep measures and investigating mechanisms is needed to support these conclusions.