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PEDIATRICS

Biomarkers of Alzheimer Disease in Children with Obstructive Sleep Apnea: Effect of Adenotonsillectomy

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Study Objective: Obese children are at increased risk for developing obstructive sleep apnea (OSA), and both of these conditions are associated with an increased risk for end-organ morbidities. Both OSA and obesity (OB) have been associated with increased risk for Alzheimer disease (AD). This study aimed to assess whether OSA and OB lead to increased plasma levels of 2 AD markers amyloid β protein 42 (Aβ42) and pre-senilin 1 (PS1).

Methods: Fasting morning plasma samples from otherwise healthy children with a diagnosis of OB, OSA, or both (OSA+OB), and controls, and in a subset of children with OSA after adenotonsillectomy (T&A) were assayed for Aβ42 and PS1 levels using commercial enzyme-linked immunosorbent assay kits.

Results: 286 children (mean age of 7.2 ± 2.7 y) were evaluated. Compared to control subjects, OB children had similar Aβ42 (108.3 ± 31.7 pg/mL versus 83.6 ± 14.6 pg/mL) and PS1 levels (0.89 ± 0.44 ng/mL versus 0.80 ± 0.29 pg/mL). However, OSA children (Aβ42: 186.2 ± 66.7 pg/mL; P < 0.001; PS1: 3.42 ± 1.46 ng/mL; P < 0.001), and particularly OSA+OB children had significant elevations in both Aβ42 (349.4 ± 112.9 pg/mL; P < 0.001) and PS1 (PS1: 4.54 ± 1.16 ng/mL; P < 0.001) circulating concentrations. In a subset of 24 children, T&A resulted in significant reductions of Aβ42 (352.0 ± 145.2 versus 151.9 ± 81.4 pg/mL; P < 0.0001) and PS1 (4.82 ± 1.09 versus 2.02 ± 1.18 ng/mL; P < 0.0001).

Conclusions: Thus, OSA, and particularly OSA+OB, are associated with increased plasma levels of AD biomarkers, which decline upon treatment of OSA in a representative, yet not all- encompassing subset of patients, suggesting that OSA may accelerate AD-related processes even in early childhood. However, the cognitive and overall health-related implications of these findings remain to be defined.

Keywords: sleep apnea, Alzheimer disease, beta-amyloid, children, inflammation, intermittent hypoxia, obesity, pre-senilin 1, sleep apnea

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Significance

Obstructive sleep apnea in children is quite prevalent, particularly in obese children. This condition is associated with cognitive deficits indicating the presence of neuronal dysfunction. Since disrupted sleep has been associated with elevations in Alzheimer Disease-related proteins in neurons, we examined whether plasma levels of 2 of such proteins were altered in children. Both amyloid β protein 42 and pre-senilin 1 were increased in children with OSA, especially in obese children with OSA, and were reduced after treatment. Future studies will need to assess whether these markers are associated with increased neurocognitive risk.

INTRODUCTION

Obesity (OB) is a frequent condition in children that carries a substantial risk for a variety of neurocognitive, cardiovascular, and metabolic complications. Similarly, obstructive sleep apnea (OSA) is a prevalent pediatric disorder that is typically associated with a higher risk for the same morbid consequences as those reported for OB. Furthermore, children with OB are at significantly increased risk for OSA.[1,2] In a previous study, it was shown that the presence of apolipoprotein ε4 allele in children with OSA, a risk factor for Alzheimer disease (AD) and atherosclerosis, markedly increased the susceptibility for neurocognitive deficits.[3] Furthermore, similar findings were present in murine models of OSA.[4,5] A recent study in children further indicated that the serum levels of AD markers, namely amyloid β 42 (Aβ42) and pre-senilin 1 (PS1) were elevated among obese adolescents, particularly when insulin resistance was concurrently present.[6]

AD is the most frequent cause of dementia worldwide, and is characterized by progressive deterioration in cognition, function, and behavior, placing a considerable burden on society.[7] The pathological hallmarks of the disease are senile plaques consisting of neurofibrillary tangles and amyloid β 42 (Aβ42) protein aggregates originating from the cleavage of the amyloid precursor protein (APP) by the APP cleaving enzyme 1 and γ-secretase, with pre-senilin 1 constituting the most prominent protease responsible for γ-secretase activity.[8,9] Approximately 25% to 40% of patients with mild and moderate AD have sleep problems and OSA is present in up to 50%.[10–13] There is a bi-directional relationship between sleep disturbance and AD.[14] In preclinical subjects, sleep fragmentation increases expression of Aβ42, the main hallmark of AD, and similarly hypoxia facilitates the pathogenesis of AD through multiple mechanisms such as increasing Aβ42 generation, stimulating the hyperphosphorylation of tau and impairing blood-brain barrier function.[15–17] Because both hypoxia and sleep fragmentation are present in OSA, we hypothesized that OSA in children may increase the circulating levels of both Aβ42 and PS1, particularly among children with OB, and that treatment of OSA may reduce Aβ42 and PS1 plasma concentrations.[18]

METHODS

Subjects

The study was approved by the human subject committee of each of the participating centers (University of Chicago IRB Protocol # #09-115-B and Comité Ético de Investigación Clínica del Área de Salud de Burgos y Soria protocol # 603), and informed consent was obtained from the legal caregiver of each participant. Assent was obtained from children at least age 7 y. Consecutive, otherwise healthy obese or nonobese prepubertal children (ages 4–12 y) from the community, and children being evaluated for habitual snoring in whom OSA

was polysomnographically diagnosed \were invited to participate between October 2013 and September 2014. All participants underwent baseline anthropometric assessments, as well as overnight polysomnography, which were interpreted using standard approaches. According to our recruitment strategies, four distinctly different groups of children were identified: controls: healthy nonsnoring children with normal polysomnographic test, body mass index (BMI) Z-score ≤ 1.34.; obese children (OB), i.e., BMI z score ≥ 1.65 but normal polysomnographic test; OSA: snoring children with abnormal polysomnographic findings confirming the presence of OSA and BMI Z-score ≤ 1.34.; OSA+OB, i.e., obese children (BMI Z-score ≥ 1.65) with polysomnographic evidence of OSA.

Exclusion Criteria

Children found to be hypertensive or using antihypertensive drug therapies were excluded (n = 17). Furthermore, children with either known or suspected diabetes, as delineated by the Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence (http://www.idf.org/sites/default/files/Diabetes-in-Childhood-and-Adolescence-Guidelines.pdf; fasting serum glucose ≥ 120 mg/dL; n = 19), with a craniofacial, neuromuscular, or defined genetic syndrome, and children on chronic anti-inflammatory therapy (n = 13), or with any known acute or chronic illness were also excluded.

Anthropometry

Height was measured with a stadiometer and recorded to the nearest 0.1 cm. Weight was recorded to the nearest 0.1 kg. Height and weight centiles were calculated using the Centers for Disease Control and Prevention 2000 growth charts for the United States. BMI Z-scores were calculated using The Children's Hospital of Philadelphia BMI and Z-score calculation in children online software (http://stokes.chop.edu/web/zscore). A BMI Z-score > 1.65 was considered as fulfilling the criteria for OB. To avoid any overlap between obese children and those with OSA or controls, the latter two groups were restricted to those children with a BMI Z-score ≤ 1.65 and ≤ 1.34, respectively.

Sphygmomanometry

All children had arterial blood pressure measured noninvasively using an automated mercury sphygmomanometer (Welch Allyn, NY) at the brachial artery using a guidelines-defined appropriate cuff size on the nondominant arm.[19] Blood pressure measurements were made in the morning after the sleep study with three consecutive measurements being performed and the average retained. Systolic blood pressure (BP) and diastolic BP indices (SBPi and DBPi, respectively) were calculated by dividing the average systolic and diastolic pressure by the respective 95th percentile for BP using National Heart, Lung, and Blood Institute guidelines (www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm), computed for age, sex, and height. Hypertension was defined when the SBPi or DBPi was > 1.

Overnight Polysomnography

Polysomnography was conducted and scored using previously described standard approaches,[20,21] and an obstructive apnea-hypopnea index (AHI) > 2/h total sleep time (TST) along with a nadir saturation of peripheral oxygen (SpO_2) < 92% and/or a respiratory arousal index (RAI) > 2/h TST served as criteria for the diagnosis of OSA.

Blood Tests

Fasting blood samples were drawn by venipuncture in the morning immediately after polysomnographic testing, and plasma samples were processed and stored at −80°C until assay. Aβ42 and PS1 concentrations were examined using commercially available enzyme-linked immunosorbent assay kits (Life Technologies cat# KHB3442, Grand Island, NY and Ray Biotech, cat#ELH-PSEN1-5, Norcross, GA). Minimal detectable concentrations were 10.0 pg/mL (linear range: 15.6–1,000 pg/mL) and 0.1 ng/mL (linear range: 0.11–15.0 ng/mL), and intra-assay coefficients of variance were 10% and 12%, respectively.

Data Analysis

Results are presented as means ± standard deviation (SD), unless stated otherwise. All numerical data were subjected to assessments of normality distribution using the Shapiro-Wilk test and to statistical analysis using independent Student *t*-tests or analysis of variance followed by *post hoc* tests (Tukey) as appropriate. Chi square analysis was performed on categorical data concerning demographic characteristics of the various groups. Pearson correlation testing was conducted to establish association between several study parameters, including Aβ42 and PS1 plasma concentrations and BMI Z-score, AHI, nadir SpO_2, oxygen desaturation index (ODI) 3%, and RAI. However, because visual inspection of the data plots suggested potential improved fits using asymptotic functions, curve fitting exploratory assessments were performed using commercially available software (Origin Pro 2015, OriginLab Corp, Northampton, MA). Statistical analyses were performed using SPSS software (version 21.0, SPSS Inc., Chicago, IL). For all comparisons, a two-tailed $P < 0.05$ was considered to define statistical significance.

RESULTS

A total of 286 children (mean age of 7.2 ± 2.7 y) completed the study, with 238 from Chicago, IL, USA and the remainder from the Burgos in Spain. Their demographic and polysomnographic characteristics are provided in Table 1. There were no demographic or anthropometric differences between Spanish children and children from the Chicago site, and their distribution in either polysomnographic findings or AD-related markers were similar. OB and control children had similar Aβ42 and PS1 levels, even if there was a trend toward slightly higher levels in children with OB, with some children with OB exhibiting levels > 3 SD beyond the mean of controls (Table 1; Figure 1A and 1B). However, children with OSA, and particularly OSA+OB children, had significant elevations in both Aβ42 and PS1 plasma concentrations (Table 1; Figure 1A and 1B). Of note, both Aβ42 and PS1 plasma levels were normally distributed. There were no significant associations between Aβ42 or PS1 levels and corresponding age, sex, ethnicity (White Caucasian versus African American) or BMI Z-scores. However,

Table 1—General characteristics of obese children and lean children with obstructive sleep apnea, obese children without obstructive sleep apnea, and healthy controls.

	OB (n = 63)	OSA+OB (n = 105)	OSA (n = 74)	Control (n = 44)
Age (y)	7.1 ± 2.6	7.2 ± 2.3	6.9 ± 2.8	6.8 ± 2.2
Sex (male, %)	55.5	48.6	59.5	50
Ethnicity				
Caucasian (%)	34.9	40.0	41.8	45.4
African-American (%)	50.7	51.4	50.0	52.3
Other	14.4	8.6	8.2	2.3
BMI Z-score	1.87 ± 0.24	1.99 ± 0.30	1.28 ± 0.22	1.08 ± 0.16 [a]
Systolic blood pressure (mmHg)	113.2 ± 10.6	117.8 ± 10.2	108.0 ± 10.1 [b]	102.3 ± 8.4 [a]
SBPi	0.96 ± 0.09	1.01 ± 0.14	0.93 ± 0.08 [b]	0.87 ± 0.07 [a]
Diastolic blood pressure (mmHg)	70.7 ± 8.9	71.8 ± 8.8	66.9 ± 7.3	63.4 ± 6.7 [a]
DBPi	0.98 ± 0.14	1.03 ± 0.16	0.92 ± 0.08	0.81 ± 0.06 [a]
Obstructive AHI (events/h)	0.9 ± 0.5	18.6 ± 16.9 [c]	14.6 ± 12.4 [c]	0.4 ± 0.2
SpO_2 Nadir (%)	93.2 ± 3.3	71.2 ± 9.5 [c]	76.7 ± 11.6 [c]	94.1 ± 2.9
ODI 3% (/h TST)	0.4 ± 0.2	18.5 ± 18.7 [c]	11.6 ± 10.6 [c]	0.2 ± 0.2
Total arousal index (/h TST)	8.9 ± 3.7	18.1 ± 6.8 [c]	17.2 ± 5.2 [c]	7.3 ± 2.8
RAI (/h TST)	0.4 ± 0.3	5.6 ± 2.7 [c]	4.4 ± 2.5 [c]	0.2 ± 0.1
Aβ42 (pg/mL)	108.3 ± 31.7	349.4 ± 112.9 [c]	186.2 ± 66.7 [b,c]	83.6 ± 14.6
PS1 (ng/mL)	0.89 ± 0.44	4.54 ± 1.16 [c]	3.42 ± 1.46 [b,c]	0.80 ± 0.29

Data are shown as mean ± SD. [a] P < 0.05 control versus all other groups; [b] P < 0.05 OSA versus OB groups; [c] P < 0.001 OSA groups versus non-OSA groups. AHI, apnea-hypopnea index; BMI, body mass index; DBPi, diastolic blood pressure index; OB, obesity; ODI 3%, oxygen desaturation index 3%; OSA, obstructive sleep apnea; RAI, respiratory arousal index; SBPi, systolic blood pressure index.

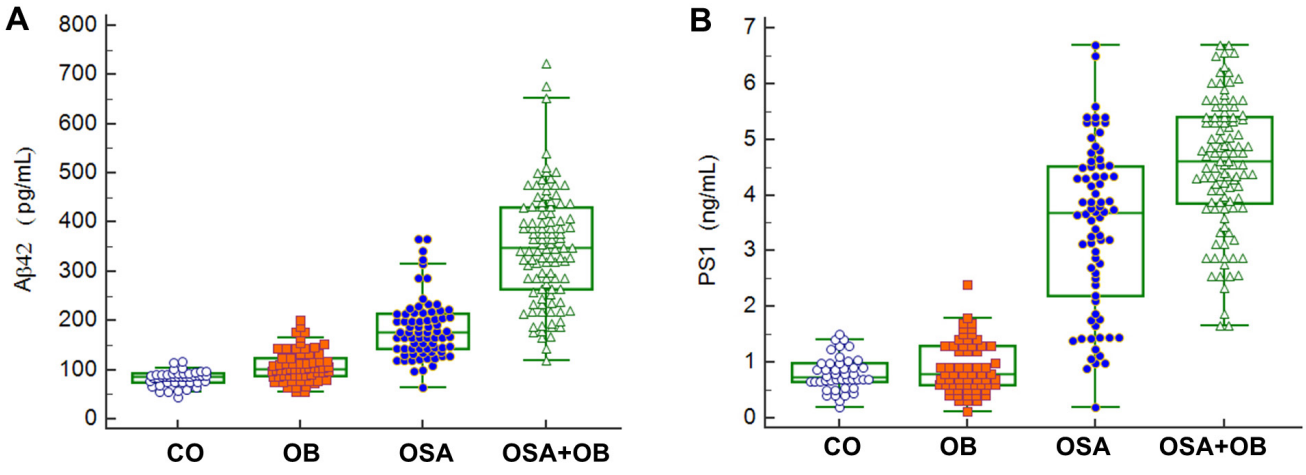

Figure 1—Individual and boxplot graphs of plasma levels of Aβ42 **(A)** and PS1 **(B)** in obese children (OB), children with OSA, children who are obese and suffer from OSA (OSA+OB) and controls (CO). Statistically significant increases in Aβ42 and PS1 serum levels emerged for OSA (P < 0.001 versus CO) and OSA+OB (P < 0.001 versus CO). In boxplots, lines and whiskers represent the medians and interquartile ranges.

significant correlations emerged between Aβ42 circulating levels and conventional measures of OSA severity, such as AHI, ODI 3%, and RAI (Figure 2A). Indeed, the Pearson coefficients of correlation between Aβ42 and AHI, ODI 3%, and RAI were 0.72, 0.66, and 0.80, respectively (P < 0.0001 for all; Figure 2A). Similarly, the coefficients of correlation between PS1 plasma levels and sleep measures were 0.74 for AHI, 0.67 for ODI 3%, and 0.89 for RAI (P < 0.0001 for all, Figure 2B). Of note, curve-fitting functions for PS1 and either AHI or ODI 3% indicated that the linear increases appeared to reach asymptotic values around AHI of 30–35/h TST, such that asymptotic curve-fitting procedures achieved improved degrees of fit (r^2: 0.86; P < 0.00001) or ODI 3% of 40/h TST (r^2: 0.87; P < 0.0001). In contrast, the linearity of the relationship between PS1 and RAI remained stable across all degrees of sleep fragmentation severity.

A subset of 24 children (11 nonobese and 13 obese) of the 35 invited to participate and return for a follow-up polysomnogram 3 to 4 mo after surgical treatment completed the second stage of the study. There were no demographic or polysomnographic

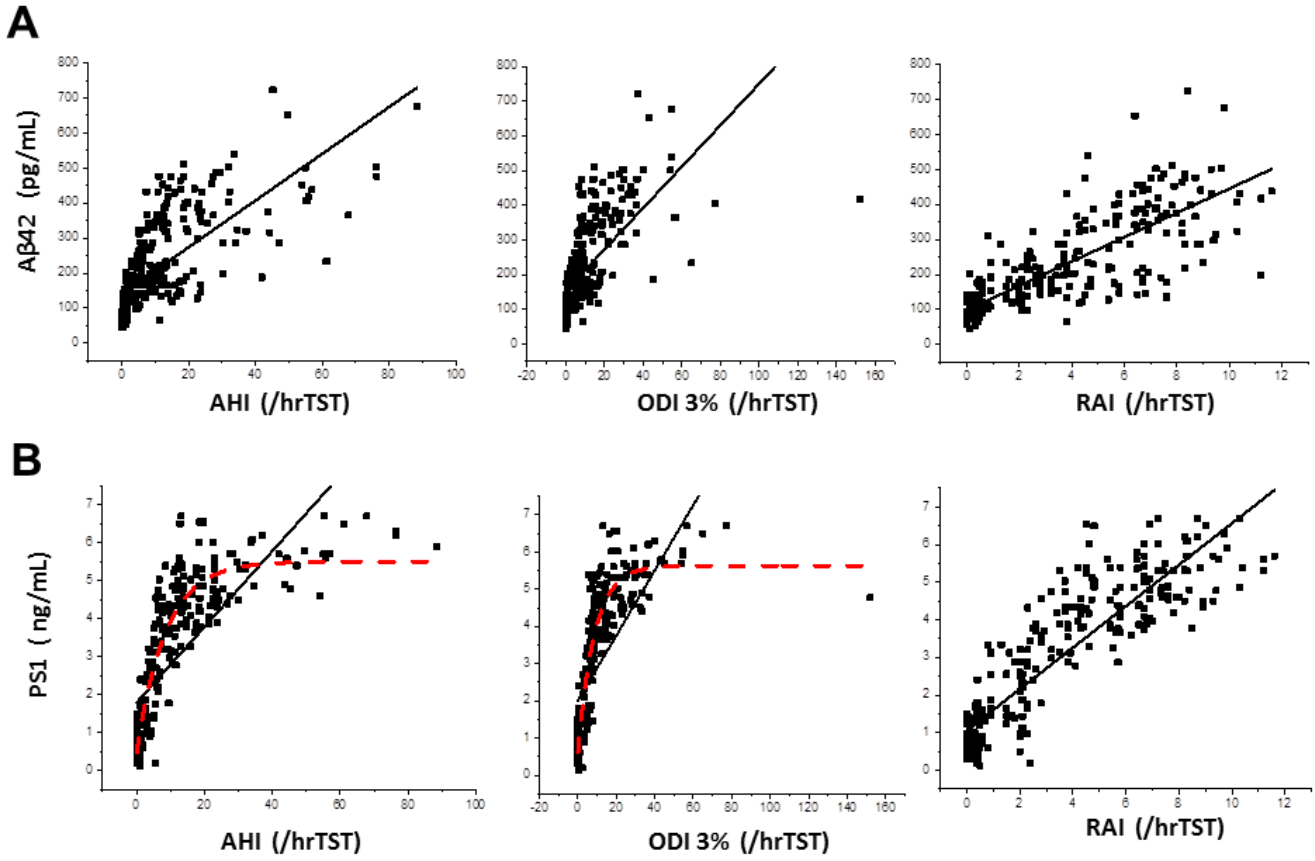

Figure 2—Scattergrams of Aβ42 **(A)** and PS1 **(B)** individual serum levels plotted against apnea-hypopnea index (AHI), oxyhemoglobin desaturation 3% index (ODI 3%), and respiratory arousal index (RAI) in 286 children. Linear regression lines are shown as solid lines whereas asymptotic regression lines are shown as dotted lines (see text for further details).

differences between these 24 children and the 11 who refused to participate. We should remark that the 35 children who were invited were those who were slated to undergo adenotonsillectomy at the University of Chicago Comer Children's Hospital. All the other children were referred for polysomnography from the community by their primary care or ear, nose, and throat physicians and were not specifically approached since this assessment was not part of the original study protocol. OSA after adenotonsillectomy (T&A) resulted in not only significant improvements in the severity of sleep-disordered breathing (Table 2; Figure 3A–3C), but significant reductions in Aβ42 (Table 2; Figure 3D; paired *t*-test: $P < 0.0001$) and PS1 (Table 2; Figure 3E; paired *t*-test: $P < 0.0001$) also emerged (see also Figure S1 in the supplemental material).

DISCUSSION

This study shows that in children the presence of OSA, rather than the presence of obesity, promotes increases in Aβ42 and PS1 levels that exhibit OSA severity-dependency associations. Furthermore, in a limited subset of children we found that treatment of OSA with surgical T&A leads to reductions in Aβ42 and PS1 levels.

Before we discuss the potential significance of our findings, some technical and methodological issues deserve comment. First and foremost, the cellular sources of the plasma Aβ42 levels measured in the current study are unclear. The wide variety of Aβ species that are detected in the cerebrospinal fluid and the central nervous system (CNS) interstitial fluid do necessarily originate in the CNS, and because passage of Aβ through the blood-brain barrier (BBB) is limited, the contribution of CNS-derived Aβ42 to the elevated plasma levels identified herein is unclear. Notwithstanding, we should remark that both the sleep fragmentation and intermittent hypoxia that characterize OSA have been implicated in disruption of the BBB, such that it is possible that Aβ42 may have indeed originated from the CNS in patients with OSA.[22–26] This is further possible when considering that concurrent obesity exacerbates the BBB disruption process, as illustrated by the more marked increases in both Aβ42 and PS1 among OSA+OB subjects.[27] In addition, we should point out that Aβ in plasma and blood does not originate only in the brain, because plasma level also reflects the virtually ubiquitous presence of APP metabolism in nearly every peripheral tissue.[28,29] Among cells within the vascular compartment, platelets release APP and Aβ42, particularly when activated,[30] and such activation is especially enhanced in OSA.[31,32] It is also possible that liver or renal dysfunction, both of which have been implicated in OSA,[33,34] and constitute the major routes for elimination of plasma Aβ42,[35,36] may also reduce the systemic clearance of Aβ42, therefore resulting in increased levels. Finally, we did not examine the

Table 2—Adenotonsillectomy treatment outcomes of 24 children with obstructive sleep apnea.

	OSA		
	Pre-T&A (n = 24)	**Post-T&A**	**P value**
Age (y)	6.8 ± 2.9	7.7 ± 3.3	
Sex (male, %)	50		
Ethnicity			
Caucasian (%)	50		
African-American (%)	50		
BMI Z-score (13 of 24 were obese with BMI Z-score > 1.65)	1.41 ± 0.42	1.45 ± 0.48	
Systolic blood pressure (mmHg)	111.2 ± 14.1	106.8 ± 12.7	< 0.04
SBPi	0.95 ± 0.12	0.91 ± 0.10	
Diastolic blood pressure (mmHg)	68.7 ± 9.3	64.2 ± 8.7	< 0.04
DBPi	0.93 ± 0.11	0.88 ± 0.08	
Obstructive AHI (events/h)	22.2 ± 15.4	2.9 ± 2.3	< 0.0001
SpO_2 Nadir (%)	75.9 ± 13.4	91.8 ± 6.9	< 0.0001
ODI 3% (/h TST)	22.8 ± 18.3	3.3 ± 3.1	< 0.0001
Total arousal index (/h TST)	18.2 ± 7.4	12.1 ± 6.8	< 0.01
RAI (/h TST)	4.3 ± 2.4	1.9 ± 1.9	< 0.0001
Aβ42 (pg/mL)	352.0 ± 145.2	151.9 ± 81.4	< 0.0001
PS1 (ng/mL)	4.82 ± 1.09	2.02 ± 1.18	< 0.0001

Data are shown as mean ± SD. AHI, apnea-hypopnea index; BMI, body mass index; DBPi, diastolic blood pressure index; OB, obesity; ODI 3%, oxygen desaturation index 3%; OSA, obstructive sleep apnea; RAI, respiratory arousal index; SBPi, systolic blood pressure index.

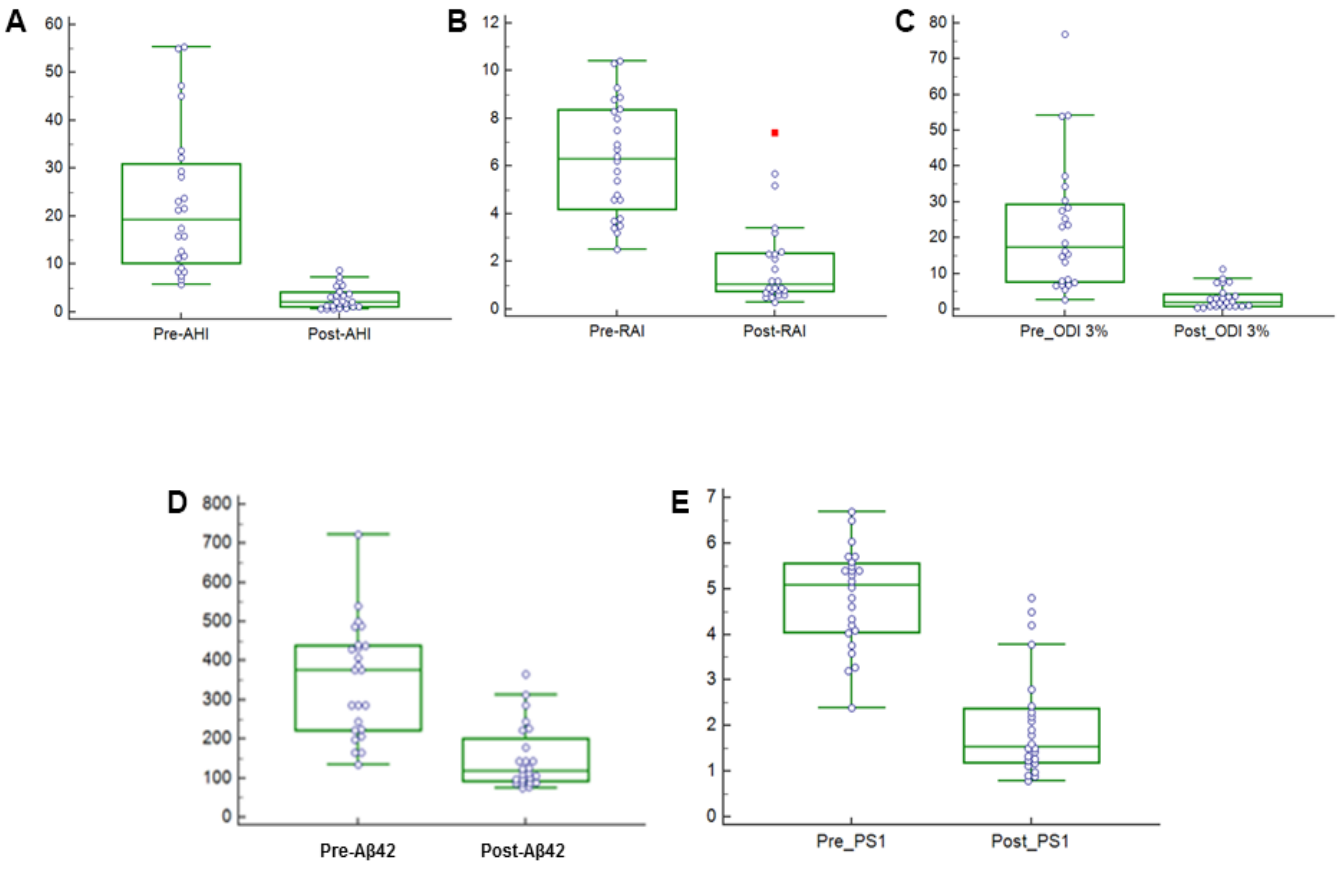

Figure 3—Individual and boxplot graphs of apnea-hypopnea index (AHI) **(A)**, oxyhemoglobin desaturation 3% index (ODI 3%) **(B)**, respiratory arousal index (RAI) **(C)**, serum levels of Aβ42 **(D)** and PS1 **(E)** in 24 children with OSA before and after adenotonsillectomy illustrating significant declines in all measures after treatment (pre- versus post: P < 0.0001 for all measures) (see also Figure S1 in the supplemental material). In boxplots, lines and whiskers represent the medians and interquartile ranges.

potential contribution of diet, a factor that has been implicated in AD risk.[37] Despite all aforementioned considerations and the inherent inability to identify the source of Aβ42, the increased presence of elevations in the plasma levels of both of these AD markers suggests a potential mechanistic relationship between OSA and these markers, which is further exacerbated by concurrent obesity. We explored the effect of treatment in only a relatively small number of subjects with OSA treated with T&A and did not include any of the children without OSA for a second assessment to ascertain that the levels of Aβ42 and PS1 remain stable over time. In addition, even though there were no discernible differences between those returning for follow-up assessments and those who did not, the restricted participation is clearly a limitation.

The measurement of AD-related markers, such as those employed in the current study, has not been extensively reported in children. Evidence has emerged on the presence of increased levels of these biomarkers in Down syndrome (a condition with a markedly elevated prevalence of OSA),[38–40] in autism spectrum disorder, particularly among patients with severe developmental delay and aggressive behaviors,[41] and among offspring of families with a high AD genetic risk.[42] In a recent study from Italy, Luciano and colleagues reported on the increased concentrations in serum of both Aβ42 and PS1 in obese adolescents, particularly those with insulin resistance.[6] These investigators did not find any BMI-related differences among younger preschool children, but in contrast found increases in levels with age.[6] In our study, the levels of AD-related biomarkers in healthy controls and in obese children without OSA were strikingly similar to those found in younger subjects by Luciano et al., but our normative data as included in the present study are limited to the age ranges assessed.[6] The current study suggests a role for OSA to causally induce alterations in Aβ42 and PS1 levels. OSA has now been strongly associated with both neurocognitive dysfunction and metabolic perturbations (i.e., insulin resistance) in prepubertal children,[43–46] which are further exacerbated by the concurrent presence of OB, the latter potentially operating as an independent and synergistic contributor.[47–50] Here, we did not evaluate cognitive function or assess insulin sensitivity, such that the implications and potential associations between Aβ42 and PS1 levels and these morbidities remains unclear. Furthermore, the genetic risk for AD in the current cohort is unknown. However, based on the deleterious effects of OSA constitutive elements, namely sleep fragmentation and intermittent hypoxia, on AD clinical course,[10–14] it is possible that the oxidative stress and inflammatory burden imposed by OSA may facilitate the increased formation of Aβ42 and other deleterious APP-derived peptides, ultimately having an effect on cognitive and metabolic function.[51,52] The uniquely elevated coefficients correlation reflecting the strong associations between intermittent hypoxia (i.e., ODI 3%) and sleep fragmentation (i.e., RAI) and AD-related biomarkers further suggest that the magnitude of metabolic degradation of APP by the activity of PS1 and other secretases into β amyloid peptides seems to be markedly increased in a severity-dependent manner in OSA, but may reach a ceiling effect, at least for PS1, in view of the asymptotic nature of the relationship between AHI or ODI 3% and this marker. Such flattening of the relationship after AHI > 30–35/h TST may signify that either a saturation of the transport of PS1 occurred or illustrate maximal effect of OSA on PS1 release.

In summary, we have shown in school-aged children that OSA induces elevations in AD-related peripheral markers such as Aβ42 and PS1. The increases in these biomarkers are further exacerbated by the concurrent presence of obesity, even if obesity alone does not incur any changes in Aβ42 and PS1 levels. Finally, treatment of OSA with adenotonsillectomy resulted in significant Aβ42 and PS1 reductions. Future exploration of potential associations between these plasma biomarkers and morbid consequences of OSA appears warranted.

ABBREVIATIONS

AD, Alzheimer disease
AHI, apnea-hypopnea index
APP, precursor protein
BBB, blood brain barrier
BMI, body mass index
OSA, obstructive sleep apnea
OB, obese
Tx, adenotonsillectomy
TAI, respiratory arousal index
ODI3%, oxyhemoglobin desaturation index 3%.

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